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UTILITY PATENT APPLICATION TRANSMITTAL *(Only for new nonprovisional applications under 37 CFR 1 53(b))*		
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	First Inventor or Application Identifier	Michelle A.J. PALMER, et al
	Title	RECEPTOR FUNCTION ASSAY FOR G-PROTEIN COUPLED RECEPTORS AND ORPHAN RECEPTORS BY REPORTER ENZYME MUTANT COMPLEMENTATION

APPLICATION ELEMENTS
See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents
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1. ■ Fee Transmittal Form (e.g. PTO/SB/17)
   (Submit an original and a duplicate for fee processing)
2. ■ Specification — Total Pages **25**
3. ■ Drawing(s) *(35 U.S.C. 113)* — Total Sheets **66**
4. □ Oath or Declaration — Total Pages
   a. □ Newly executed (original or copy)
   b. □ Copy from a prior application *(37 C.F.R. §1.63(d))*
   (for continuation/divisional with box 15 completed)
      i. □ DELETION OF INVENTOR(S)
      Signed statement attached deleting inventor(s) named in the prior application, see *37 C.F.R. §1.63(d)(2) and 1.33(b).*
5. □ Incorporation By Reference *(usable if box 4B is checked)*
   The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4B, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

ACCOMPANYING APPLICATION PARTS

6. □ Assignment Papers (cover sheet & document(s))
7. □ 37 C.F.R. §3.73(b) Statement *(when there is an assignee)* □ Power of Attorney
8. □ English Translation Document *(if applicable)*
9. □ Information Disclosure Statement (IDS)/PTO-1449 □ Copies of IDS Citations
10. □ Preliminary Amendment
11. ■ White Advance Serial No. Postcard
12. □ Small Entity Statement(s) □ Statement filed in prior application. Status still proper and desired.
13. □ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*
14. ■ Other: List of Inventors' Names and Addresses

15. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below:*
□ Continuation □ Divisional □ Continuation-in-part (CIP) of prior application no.:
Prior application information: Examiner: Group Art Unit:

16. Amend the specification by inserting before the first line the sentence:
□ This application is a □ Continuation □ Division □ Continuation-in-part (CIP) of application Serial No. Filed on

■ This application claims priority of provisional application Serial No. 60/180,669 Filed February 7, 2000

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Docket No. 4085-226-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTOR(S) Michelle A.J. PALMER, et al

SERIAL NO: New Application

FILING DATE: Herewith

FOR: RECEPTOR FUNCTION ASSAY FOR G-PROTEIN COUPLED RECEPTORS AND ORPHAN RECEPTORS BY REPORTER ENZYME MUTANT COMPLEMENTATION

FEE TRANSMITTAL

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DOCKET NO: 4085-226-27

TITLE OF THE INVENTION

RECEPTOR FUNCTION ASSAY FOR G-PROTEIN COUPLED RECEPTORS AND ORPHAN RECEPTORS BY REPORTER ENZYME MUTANT COMPLEMENTATION

BACKGROUND OF THE INVENTION

This application claims the benefit from Provisional Application Serial No. 60/180,669, filed February 7, 2000. The entirety of that provisional application is incorporated herein by reference.

Field of the Invention

This invention relates to methods of detecting G-protein-coupled receptor (GPCR) activity, and provides methods of assaying GPCR activity and methods for screening for GPCR ligands, G-protein-coupled receptor kinase (GRK) activity, and compounds that interact with components of the GPCR regulatory process.

The actions of many extracellular signals are mediated by the interaction of G-protein-coupled receptors (GPCRs) and guanine nucleotide-binding regulatory proteins (G-proteins). G-protein-mediated signaling systems have been identified in many divergent organisms, such as mammals and yeast. The GPCRs represent a large super family of proteins which have divergent amino acid sequences, but share common structural features, in particular, the presence of seven transmembrane helical domains. GPCRs respond to, among other extracellular signals, neurotransmitters, hormones, odorants and light. Individual GPCR types activate a particular signal transduction pathway; at least ten different signal transduction pathways are known to be activated via GPCRs. For example, the beta 2-adrenergic receptor (β2AR) is a prototype mammalian GPCR. In response to agonist binding, β2AR receptors activate a G-protein (Gs) which in turn stimulates adenylate cyclase activity and results in increased cyclic adenosine monophosphate (cAMP) production in the cell.

The signaling pathway and final cellular response that result from GPCR stimulation depends on the specific class of G-protein with which the particular receptor is coupled (Hamm, "The many faces of G-Protein Signaling." J. Biol. Chem., 273:669-672 (1998)). For instance, coupling to the Gs class of G-proteins stimulates cAMP production and activation of Protein Kinase A and C pathways, whereas coupling to the Gi class of G-proteins down regulates cAMP. Other second messenger systems as calcium, phosphlipase C, and phosphatidylinositol 3 may also be utilized. As a consequence, GPCR signaling events have predominantly been measured via quantification of these second messenger products.

A common feature of GPCR physiology is desensitization and recycling of the receptor through the processes of receptor phosphorylation, endocytosis and dephosphorylation (Ferguson, et al., "G-protein-coupled receptor regulation: role of G-protein-coupled receptor kinases and arrestins." Can. J. Physiol. Pharmacol., 74:1095-1110 (1996)). Ligand-occupied GPCRs can be phosphorylated by two families of serine/threonine kinases, the G-protein-coupled receptor kinases (GRKs) and the second messenger-dependent protein kinases such as protein kinase A and protein kinase C. Phosphorylation by either class of kinases serves to down-regulate the receptor by uncoupling it from its corresponding G-protein. GRK-phosphorylation also serves to down-regulate the receptor by recruitment of a class of proteins known as the arrestins that bind the cytoplasmic domain of the receptor and promote clustering of the receptor into endocytic vescicles. Once the receptor is endocytosed, it will either be degraded in lysosomes or dephosphorylated and recycled back to the plasma membrane as fully-functional receptor.

Binding of an arrestin protein to an activated receptor has been documented as a common phenomenon for a variety of GPCRs ranging from rhodopsin to β2AR to the

neurotensin receptor (Barak, et al., "A β-arrestin/Green Fluorescent fusion protein biosensor for detecting G-Protein-Coupled Receptor Activation," J. Biol. Chem., 272:27497-500 (1997)). Consequently, monitoring arrestin interaction with a specific GPCR can be utilized as a generic tool for measuring GPCR activation. Similarly, a single G-protein and GRK also partner with a variety of receptors (Hamm, et al. (1998) and Pitcher et al., "G-Protein-Coupled Receptor Kinases," Annu. Rev. Biochem., 67:653-92 (1998)), such that these protein/protein interactions may also be monitored to determine receptor activity.

The present invention involves the use of a proprietary technology (ICAST™, Intercistronic Complementation Analysis Screening Technology) for monitoring protein/protein interactions in GPCR signaling. The method involves using two inactive β-galactosidase mutants, each of which is fused with one of two interacting protein pairs, such as a GPCR and an arrestin. The formation of an active β-galactosidase complex is driven by interaction of the target proteins. In this system, β-galactosidase activity acts as a read out of GPCR activity. FIGURE 23 is a schematic depicting the method of the present invention. FIGURE 23 shows two inactive mutants that become active when they interact. In addition, this technology could be used to monitor GPCR-mediated signaling pathways via other downstream signaling components such as G-proteins, GRKs or c-Src.

Many therapeutic drugs in use today target GPCRs, as they regulate vital physiological responses, including vasodilation, heart rate, bronchodilation, endocrine secretion and gut peristalsis. See, e.g., Lefkowitz et al., Annu. Rev. Biochem., 52:159 (1983). For instance, drugs targeting the highly studied GPCR, β2AR are used in the treatment of anaphylaxis, shock hypertension, asthma and other conditions. Some of these drugs mimic

the ligand for this receptor. Other drugs act to antagonize the receptor in cases when disease arises from spontaneous activity of the receptor.

Efforts such as the Human Genome Project are identifying new GPCRs ("orphan" receptors) whose physiological roles and ligands are unknown. It is estimated that several thousand GPCRs exist in the human genome. Of the 250 GPCRs identified to date, only 150 have been associated with ligands.

SUMMARY OF THE INVENTION

A first aspect of the present invention is a method that monitors GPCR function proximally at the site of receptor activation, thus providing more information for drug discovery purposes due to fewer competing mechanisms. Activation of the GPCR is measured by a read-out for interaction of the receptor with a regulatory component such as arrestin, G-protein, GRK or other kinases, the binding of which to the receptor is dependent upon agonist occupation of the receptor. Protein/protein interaction is detected by complementation of reporter proteins such as utilized by the ICAST™ technology.

A further aspect of the present invention is a method of assessing G-protein-coupled receptor (GPCR) pathway activity under test conditions by providing a test cell that expresses a GPCR, e.g., muscarinic, adrenergic, dopamine, angiotensin or endothelin, as a fusion protein to a mutant reporter protein and interacting, i.e., G-proteins, arrestin or GRK, as a fusion protein with a complementing reporter protein. When test cells are exposed to a known agonist to the target GPCR under test conditions, activation of the GPCR will be monitored by complementation of the reporter enzyme. Increased reporter enzyme activity reflects interaction of the GPCR with its interacting protein partner.

A further aspect of the present invention is a method of assessing GPCR pathway activity in the presence of a test kinase.

A further aspect of the present invention is a method of assessing GPCR pathway activity in the presence of a test G-protein.

A further aspect of the present invention is a method of assessing GPCR pathway activity upon exposure of the test cell to a test ligand.

A further aspect of the present invention is a method of assessing GPCR pathway activity upon co-expression in the test cell of a second receptor.

A further aspect of the present invention is a method for screening for a ligand or agonists to an orphan GPCR. The ligand or agonist could be contained in natural or synthetic libraries or mixtures or could be a physical stimulus. A test cell is provided that expresses the orphan GPCR as a fusion protein with one β-galactosidase mutant and, for example, an arrestin or mutant form of arrestin as a fusion protein with another β-galactosidase mutant. The interaction of the arrestin with the orphan GPCR upon receptor activation is measured by enzymatic activity of the complemented β-galactosidase. The test cell is exposed to a test compound, and an increase in β-galactosidase activity indicates the presence of a ligand or agonist.

A further aspect of the present invention is a method for screening a protein of interest, for example, an arrestin protein (or mutant form of the arrestin protein) for the ability to bind to a phosphorylated, or activated, GPCR. A cell is provided that expresses a GPCR and contains β-arrestin. The cell is exposed to a known GPCR agonist and then reporter enzyme activity is detected. Increased reporter enzyme activity indicates that the β-arrestin molecule can bind to phosphorylated, or activated, GPCR in the test cell.

A further aspect of the present invention is a method to screen for an agonist to a specific GPCR. The agonist could be contained in natural or synthetic libraries or could be a physical stimulus. A test cell is provided that expresses a GPCR as a fusion protein with one β-galactosidase mutant and, for example, an arrestin as a fusion protein with another β-galactosidase mutant. The interaction of arrestin with the GPCR upon receptor activation is measured by enzymatic activity of the complemented β-galactosidase. The test cell is exposed to a test compound, and an increase in β-galactosidase activity indicates the presence of an agonist. The test cell may express a known GPCR or a variety of known GPCRs, or may express an unknown GPCR or a variety of unknown GPCRs. The GPCR may be, for example, an odorant GPCR or a βAR GPCR.

A further aspect of the present invention is a method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity. A test cell is provided that expresses a GPCR as a fusion protein with one β-galactosidase mutant and, for example, an arrestin as a fusion protein with another β-galactosidase mutant. The interaction of arrestin with the GPCR upon receptor activation is measured by enzymatic activity of the complemented β-galactosidase. The test cell is exposed to a test compound, and an increase in β-galactosidase activity indicates the presence of an agonist. The cell is exposed to a test compound and to a GPCR agonist, and reporter enzyme activity is detected. When exposure to the agonist occurs at the same time as or subsequent to exposure to the test compound, a decrease in β-galactosidase activity after exposure to the test compound indicates that the test compound has antagonist activity to the GPCR.

A further aspect of the present invention is a method of screening a sample solution for the presence of an agonist, antagonist or ligand to a G-protein-coupled receptor (GPCR).

A test cell is provided that expresses a GPCR fusion and contains, for example, a β-arrestin protein fusion. The test cell is exposed to a sample solution, and reporter enzyme activity is assessed. Changed reporter enzyme activity after exposure to the sample solution indicates the sample solution contains an agonist, antagonist or ligand for a GPCR expressed in the cell.

A further aspect of the present invention is a method of screening a cell for the presence of a G-protein-coupled receptor (GPCR).

A further aspect of the present invention is a method of screening a plurality of cells for those cells which contain a G-protein coupled receptor (GPCR).

A further aspect of the invention is a method for mapping GPCR-mediated signaling pathways. For instance, the system could be utilized to monitor interaction of c-src with β-arrestin-1 upon GPCR activation. Additionally, the system could be used to monitor protein/protein interactions involved in cross-talk between GPCR signaling pathways and other pathways such as that of the receptor tyrosine kinases or Ras/Raf.

A further aspect of the invention is a method for monitoring homo- or hetero-dimerization of GPCRs upon agonist or antagonist stimulation.

A further aspect of the invention is a method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist. A cell is provided that contains protein partners that interact downstream in the GPCR's pathway. The protein partners are expressed as fusion proteins to the mutant, complementing enzyme and are used to monitor activation of the GPCR. The cell is exposed to a GPCR agonist and then enzymatic activity of the reporter enzyme is detected. Increased reporter enzyme activity indicates that the cell contains a GPCR responsive to the agonist.

The invention is achieved by using ICAST™ protein/protein interaction screening to map signaling pathways. This technology is applicable to a variety of known and unknown GPCRs with diverse functions. They include, but are not limited to, the following sub-families of GPCRs:

(a) receptors that bind to amine-like ligands-Acetylcholine muscarinic receptor (M1 to M5), alpha and beta Adrenoceptors, Dopamine receptors (D1, D2, D3 and D4), Histamine receptors (H1 and H2), Octopamine receptor and Serotonin receptors (5HT1, 5HT2, 5HT4, 5HT5, 5HT6, 5HT7);

(b) receptors that bind to a peptide ligand-Angiotensin receptor, Bombesin receptor, Bradykinin receptor, C-C chemokine receptors (CCR1 to CCR8, and CCR10), C-X-C type Chemokine receptors (CXC-R5), Cholecystokinin type A receptor, CCK type receptors, Endothelin receptor, Neurotesin receptor, FMLP-related receptors, Somatostatin receptors (type 1 to type 5) and Opioid receptors (type D, K, M, X);

(c) receptors that bind to hormone proteins- Follic stimulating hormone receptor, Thyrotrophin receptor and Lutropin-choriogonadotropic hormone receptor;

(d) receptors that bind to neurotransmitters-substance P receptor, Substance K receptor and neuropeptide Y receptor;

(e) Olfactory receptors-Olfactory type 1 to type 11, Gustatory and odorant receptors;

(f) Prostanoid receptors-Prostaglandin E2 (EP1 to EP4 subtypes), Prostacyclin and Thromboxane;

(g) receptors that bind to metabotropic substances-Metabotropic glutamate group I to group III receptors;

(h) receptors that respond to physical stimuli, such as light, or to chemical stimuli, such as taste and smell; and

(i) orphan GPCRs-the natural ligand to the receptor is undefined.

ICAST™ provides many benefits to the screening process, including the ability to monitor protein interactions in any sub-cellular compartment-membrane, cytosol and nucleus; the ability to achieve a more physiologically relevant model without requiring protein overexpression; and the ability to achieve a functional assay for receptor binding allowing high information content.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1. Cellular expression levels of β2 adrenergic receptor (β2AR) and β-arrestin-2 (βArr2) in C2 clones. Quantification of β-gal fusion protein was performed using antibodies against β-gal and purified β-gal protein in a titration curve by a standardized ELISA assay. Figure 1A shows expression levels of β2AR-βgalΔα clones (in expression vector pICAST ALC). Figure 1B shows expression levels of βArr2-βgalΔω in expression vector pICAST OMC4 for clones 9-3, -7, -9, -10, -19 and –24, or in expression vector pICAST OMN4 for clones 12-4, -9, -16, -18, -22 and -24.

FIGURE 2. Receptor β2AR activation was measured by agonist-stimulated cAMP production. C2 cells expressing pICAST ALC β2AR (clone 5) or parental cells were treated with increasing concentrations of (-)isoproterenol and 0.1mM IBMX. The quantification of cAMP level was expressed as pmol/well.

FIGURE 3. Interaction of activated receptor β2AR and arrestin can be measured by β-galactosidase complementation. Figure 3A shows a time course of β–galactosidase activity in response to agonist (-)isoproterenol stimulation in C2 expressing β2AR-βgalΔα (β2AR alone, in expression vector pICAST ALC), or C2 clones, and a pool of C2 co-expressing β2AR-βgalΔα and βArr2-βgalΔω (in expression vectors pICAST ALC and pICAST OMC). Figure 3B shows a time course of β galactosidase activity in response to agonist (-)isoproterenol stimulation in C2 cells expressing β2AR alone (in expression vector pICAST ALC) and C2 clones co-expressing β2AR and βArr1 (in expression vectors ICAST ALC and pICAST OMC).

FIGURE 4. Agonist dose response for interaction of β2AR and arrestin can be measured by β-galactosidase complementation. Figure 4A shows a dose response to agonists (-)isoproterenol and procaterol in C2 cells co-expressing pICAST ALC β2AR and pICAST OMC βArr2 fusion constructs. Figure 4B shows a dose response to agonists (-)isoproterenol and procaterol in C2 cells co-expressing pICAST ALC β2AR and pICAST OMC βArr1 fusion constructs.

FIGURE 5. Antagonist mediated inhibition of receptor activity can be measured by β-galactosidase complementation in cells co-expressing β2AR-βgalΔα and βArr-βgalΔω. Figure 5A shows specific inhibition with adrenergic antagonists ICI-118,551 and propranolol of β-galactosidase activity in C2 clones co-expressing pICAST ALC β2AR and pICAST OMC βArr2 fusion constructs after incubation with agonist (-)isoproterenol. Figure 5B shows specific inhibition of β-galactosidase activity with adrenergic antagonists ICI-118,551

and propranolol in C2 clones co-expressing pICAST ALC β2AR and pICAST OMC βArr1 fusion constructs in the presence of agonist (-)isoproterenol.

FIGURE 6. C2 cells expressing adenosine receptor A2a show cAMP induction in response to agonist (CGC-21680) treatment. C2 parental cells and C2 cells co-expressing pICAST ALC A2aR and pICAST OMC βArr1 as a pool or as selected clones were measured for agonist-induced cAMP response (pmol/well).

FIGURE 7. Agonist stimulated cAMP response in C2 cells co-expressing Dopamine receptor D1 (D1-βgalΔα) and β-arrestin-2 (βArr2-βgalΔω). The clone expressing βArr2-βgalΔω (Arr2 alone) was used as a negative control in the assay. Cells expressing D1-βgalΔα in addition to βArr2-βgalΔω responded agonist treatment (3-hydroxytyramine hydrochloride at 3 μM) . D1(PIC2) or D1(PIC3) designate D1 in expression vector pICAST ALC2 or pICAST ALC4, respectively.

FIGURE 8. Variety of mammalian cell lines can be used to generate stable cells for monitoring GPCR and arrestin interactions. FIGURE 8A, FIGURE 8B and FIGURE 8C show the examples of HEK293, CHO and CHW cell lines co-expressing adrenergic receptor β2AR and arrestin fusion proteins of β-galactosidase mutants. The β-galactosidase activity was used to monitor agonist-induced interaction of β2AR and arrestin proteins.

FIGURE 9. Beta-gal complementation can be used to monitor β2 adrenergic receptor homo-dimerization. FIGURE 9A shows β–galactosidase activity in HEK293 clones co-expressing pICAST ALC β2AR and pICAST OMC β2AR. FIGURE 9B shows a cAMP response to agonist (-)isoproterenol in HEK 293 clones co-expressing pICAST ALC β2AR

and pICAST OMC β2AR. HEK293 parental cells were included in the assays as negative controls.

FIGURE 10A. pICAST ALC: Vector for expression of β-galΔα as a C-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔα; GS Linker, (GGGGS)n; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 10B. Nucleotide sequence for pICAST ALC.

FIGURE 11A. pICAST ALN: Vector for expression of β-galΔα as an N-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔα; GS Linker, (GGGGS)n; NeoR, neomycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 11B. Nucleotide sequence for pICAST ALN.

FIGURE 12A. pICAST OMC: Vector for expression of β-galΔω as a C-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔω ; GS Linker, (GGGGS)n; Hygro, hygromycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 12B. Nucleotide sequence for pICAST OMC.

FIGURE 13A. pICAST OMN: Vector for expression of β-galΔω as an N-terminal fusion to the target protein. This construct contains the following features: MCS, multiple cloning site for cloning the target protein in frame with the β-galΔω; GS Linker, (GGGGS)n; Hygro, hygromycin resistance gene; IRES, internal ribosome entry site; ColE1ori, origin of replication for growth in E. coli; 5'MoMuLV LTR and 3'MoMuLV LTR, viral promotor and polyadenylation signals from the Moloney Murine leukemia virus.

FIGURE 13B. Nucleotide sequence for pICAST OMN.

FIGURE 14. pICAST ALC βArr2: Vector for expression of β-galΔα as a C-terminal fusion to β-arrestin-2. The coding sequence of human β-arrestin-2 (Genebank Accession Number: NM_004313) was cloned in frame to β-galΔα in a pICAST ALC vector.

FIGURE 15. pICAST OMC βArr2: Vector for expression of β-galΔω as a C-terminal fusion to β-arrestin-2. The coding sequence of human β-arrestin-2 (Genebank Accession Number: NM_004313) was cloned in frame to β-galΔω in a pICAST OMC vector.

FIGURE 16. pICAST ALC βArr1: Vector for expression of β-galΔα as a C-terminal fusion to β-arrestin-1. The coding sequence of human β-arrestin-1 (Genebank Accession Number: NM_004041) was cloned in frame to β-galΔα in a pICAST ALC vector.

FIGURE 17. pICAST OMC βArr1: Vector for expression of β-galΔω as a C-terminal fusion to β-arrestin-1. The coding sequence of human β-arrestin-1 (Genebank Accession Number: NM_004041) was cloned in frame to β-galΔω in a pICAST OMC vector.

FIGURE 18. pICAST ALC β2AR: Vector for expression of β-galΔα as a C-terminal fusion to β2 Adrenergic Receptor. The coding sequence of human β2 Adrenergic Receptor

(Genebank Accession Number: NM_000024) was cloned in frame to β-galΔα in a pICAST ALC vector.

FIGURE 19. pICAST OMC β2AR: Vector for expression of β-galΔω as a C-terminal fusion β2 Adrenergic Receptor. The coding sequence of human β2 Adrenergic Receptor (Genebank Accession Number: NM_000024) was cloned in frame to β-galΔω in a pICAST OMC vector.

FIGURE 20. pICAST ALC A2aR: Vector for expression of β-galΔα as a C-terminal fusion to Adenosine 2a Receptor. The coding sequence of human Adenosine 2a Receptor (Genebank Accession Number: NM_000675) was cloned in frame to β-galΔα in a pICAST ALC vector.

FIGURE 21. pICAST OMC A2aR: Vector for expression of β-galΔω as a C-terminal fusion to Adenosine 2a Receptor. The coding sequence of human Adenosine 2a Receptor (Genebank Accession Number: NM_000675) was cloned in frame to β-galΔω in a pICAST OMC vector.

FIGURE 22. pICAST ALC D1: Vector for expression of β-galΔα as a C-terminal fusion to Dopamine D1 Receptor. The coding sequence of human Dopamine D1 Receptor (Genebank Accession Number: X58987) was cloned in frame to β-galΔα in a pICAST ALC vector.

FIGURE 23. A schematic depicting the method of the invention, which shows that two inactive mutants that become active when they interact.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

All literature and patents cited in this disclosure are incorporated herein by reference.

The present invention provides a method to interrogate GPCR function and pathways. The G-protein-coupled superfamily continues to expand rapidly as new receptors are discovered through automated sequencing of cDNA libraries or genomic DNA. It is estimated that several thousand GPCRs may exist in the human genome, as many as 250 GPCRs have been cloned and only as few as 150 have been associated with ligands. The means by which these, or newly discovered orphan receptors, will be associated with their cognate ligands and physiological functions represents a major challenge to biological and biomedical research. The identification of an orphan receptor generally requires an individualized assay and a guess as to its function. The interrogation of a GPCR's signaling behavior by introducing a replacement receptor eliminates these prerequisites because it can be performed with and without prior knowledge of other signaling events. It is sensitive, rapid and easily performed and should be applicable to nearly all GPCRs because the majority of these receptors should desensitize by a common mechanism.

Various approaches have been used to monitor intracellular activity in response to a stimulant, e.g., enzyme-linked immunosorbent assay (ELISA); Fluorescense Imaging Plate Reader assay (FLIPR™, Molecular Devices Corp., Sunnyvale, CA); EVOscreen™, EVOTEC™, Evotec Biosystems Gmbh, Hamburg, Germany; and techniques developed by CELLOMICS™, Cellomics, Inc., Pittsburgh, PA.

Germino, F.J., et al., "Screening for in vivo protein-protein interactions." Proc. Natl. Acad. Sci., 90(3): 933-7 (1993), discloses an *in vivo* approach for the isolation of proteins interacting with a protein of interest.

Phizicky, E.M., et al., "Protein-protein interactions: methods for detection and analysis." Microbiol. Rev., 59(1): 94-123 (1995), discloses a review of biochemical, molecular biological and genetic methods used to study protein-protein interactions.

Offermanns, et al., "$G\alpha_{15}$ and $G\alpha_{16}$ Couple a Wide Variety of Receptors to Phospholipase C." J. Biol. Chem., 270(25):15175-80 (1995), discloses that $G\alpha_{15}$ and $G\alpha_{16}$ can be activated by a wide variety of G-protein-coupled receptors. The selective coupling of an activated receptor to a distinct pattern of G-proteins is regarded as an important requirement to achieve accurate signal transduction. Id.

Barak et al., "A β-arrestin/Green Fluorescent Protein Biosensor for Detecting G Protein-coupled Receptor Activation." J. Biol. Chem., 272(44):27497-500 (1997) and U.S. Patent No. 5,891,646, disclose the use of a β-arrestin/green fluorescent fusion protein (GFP) to monitor protein translocation upon stimulation of GPCR.

The present invention involves a method for monitoring protein-protein interactions in GPCR pathways as a complete assay using ICAST™ (Intercistronic Complementation Analysis Screening Technology as disclosed in pending U.S. patent application serial no. 053,164, filed April 1, 1998, the entire contents of which are incorporated herein by reference). This invention enables an array of assays, including GPCR binding assays, to be achieved directly within the cellular environment in a rapid, non-radioactive assay format amenable to high-throughput screening. Using existing technology, assays of this type are currently performed in a non-cellular environment and require the use of radioisotopes.

The present invention combined with Tropix ICAST™ and Advanced Discovery Sciences™ technologies, e.g., ultra high-throughput screening, provide highly sensitive cell-based methods for interrogating GPCR pathways which are amendable to high-throughput

screening (HTS). These methods are an advancement over the invention disclosed in U.S. Patent 5,891,646, which relies on microscopic imaging of GPCR components as fusion with Green-fluorescent-protein. Imaging techniques are limited by low-throughput, lack of thorough quantification and low signal to noise ratios. Unlike yeast-based-2-hybrid assays used to monitor protein/protein interactions in high-throughput assays, the present invention is applicable to a variety of cells including mammalian cells, plant cells, protozoa cells such as E. coli and cells of invertebrate origin such as yeast, slime mold (*Dictyostelium*) and insects; detects interactions at the site of the receptor target or downstream target proteins rather than in the nucleus; and does not rely on indirect read-outs such as transcriptional activation. The present invention provides assays with greater physiological relevance and fewer false negatives.

Advanced Discovery Sciences™ is in the business of offering custom-developed screening assays optimized for individual assay requirements and validated for automation. These assays are designed by HTS experts to deliver superior assay performance. Advanced Discovery Sciences'™ custom assay development service encompasses the design, development, optimization and transfer of high performance screening assays. Advanced Discovery Sciences™ works to design new assays or convert existing assays to ultra-sensitive luminescent assays ready for the rigors of HTS. Among some of the technologies developed by Advanced Discovery Sciences™ are the cAMP-Screen™ immunoassay system. This system provides ultrasensitive determination of cAMP levels in cell lysates. The cAMP-Screen™ assay utilizes the high-sensitivity chemiluminescent alkaline phosphatase (AP) substrate CSPD® with Sapphire-II™ luminescence enhancer.

EXAMPLE:

GPCR activation can be measured through monitoring the binding of ligand-activated GPCR by an arrestin. In this assay system, a GPCR, e.g. β adrenergic receptor (β 2AR) and a β arrestin are co-expressed in the same cell as fusion proteins with β gal mutants. As illustrated in Figure 1, the β2AR is expressed as a fusion protein with Δα form of β gal mutant (β2ADRΔα) and the b arrestin as a fusion protein with the Δω mutant of β gal (β-ArrΔω). The two fusion proteins exist inside of a resting (or un-stimulated) cell in separate compartments, i.e. membrane for GPCR and cytosol for arrestin, and they can not form an active b galactosidase enzyme. When such a cell is treated with an agonist or a ligand, the ligand-occupied and activated receptor will become a high affinity binding site for Arrestin. The interaction between an activated β2ADRΔα and β–ArrΔω drives the β gal gal mutant complementation. The enzyme activity can be measured by using an enzyme substrate, which upon cleavage releases a product measurable by colorimetry, fluorescence, chemiluminescence (e.g. Tropix product GalScreenTM).

Experiment protocol-

1. In the first step, the expression vectors for β2ADRΔα and βArr2Δω were engineered in selectable retroviral vectors pICAST ALC, as described in Figure 18 and pICAST OMC, as in Figure 15.

2. In the second step, the two expression constructs were transduced into either C2C12 myoblast cells, or other mammalian cell lines, such as COS-7, CHO, A431, HEK 293, and CHW. Following selection with antibiotic drugs, stable clones expressing both fusion

proteins at appropriate levels were selected.

3. In the last step, the cells expressing both β2ADRΔα and βArr2Δω were tested for response by agonist/ligand stimulated β galactosidase activity. Triplicate samples of cells were plated at 10,000 cells in 100 microliter volume into a well of 96-well culture plate. Cells were cultured for 24 hours before assay. For agonist assay (Figure 3 and 4), cells were treated with variable concentrations of agonist, for example, (-) isoproterenol, procaterol, dobutamine, terbutiline or L-L-phenylephrine for 60 min at 37 C. The induced β galatosidase activity was measured by addition of Tropix GalScreenTM substrate (Applied Biosystems) and luminescence measured in a Tropix TR717TM luminometer (Applied Biosystems). For antagonist assay (Figure 5), cells were pre-incubated for 10 min in fresh medium without serum in the presence of ICI-118,551 or propranolol followed by addition of 10 micro molar (-) isoproterenol.

The assays of this invention, and their application and preparation have been described both generically, and by specific example. The examples are not intended as limiting. Other substituent identities, characteristics and assays will occur to those of ordinary skill in the art, without the exercise of inventive faculty. Such modifications remain within the scope of the invention, unless excluded by the express recitation of the claims advanced below.

WHAT IS CLAIMED IS:

1. A method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an interacting protein partner as a fusion to another mutant form of enzyme;

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition.

2. A method according to Claim 1, wherein the test condition is the presence in the cell of a kinase.

3. A method according to Claim 1, wherein the test condition is the presence in the cell of a G-protein.

4. A method according to Claim 1, wherein the test condition is the exposure of the cell to a compound selected from GPCR agonists and GPCR antagonists.

5. A method according to Claim 1, wherein the test condition is co-expression in the cell of a second receptor.

6. A method according to Claim 5, wherein the second receptor is a GPCR receptor.

7. A method according to Claim 5, wherein homo-dimerization of GPCR is determined.

8. A method according to Claim 5, wherein hetero-dimerization of GPCR is determined.

9. A method for screening a β-arrestin protein or an unidentified arrestin or arrestin-like protein or fragment and mutant form thereof for the ability to bind to activated GPCRs, comprising:

a) providing a cell that:

i) expresses at least one GPCR as a fusion protein to a reporter enzyme; and

ii) contains a conjugate comprising a test β-arrestin protein as a fusion protein with another reporter enzyme;

b) exposing the cell to a ligand for said at least one GPCR; and

c) detecting enzymatic activity of the complemented reporter enzyme;

wherein an increase in enzymatic activity in the cell indicates β-arrestin protein binding to the activated GPCR.

10. A method for screening a test compound for G-protein-coupled receptor (GPCR) agonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

b) exposing the cell to a test compound; and

c) detecting complementation of said reporter enzyme;

wherein increased reporter enzyme activity after exposure of the cell to the test compound indicates GPCR agonist activity of the test compound.

11. A method according to Claim 10, wherein the cell expresses a GPCR whose function is known.

12. A method according to Claim 10, wherein the cell expresses a GPCR whose function is unknown.

13. A method according to Claim 10, wherein the cell expresses an odorant or taste GPCR.

14. A method according to Claim 10, wherein the cell expresses a GPCR a β-adrenergic GPCR.

15. A method according to Claim 10, wherein the cell is selected from the group consisting of mammalian cells, cells of invertebrate origin, plant cells and protozoa cells.

16. A method according to Claim 10, wherein the cell endogenously expresses a GPCR.

17. A method according to Claim 10, wherein the cell has been transformed to express a GPCR not endogenously expressed by such a cell.

18. A method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

b) exposing the cell to said test compound;

c) exposing the cell to an agonist for said GPCR; and

d) detecting complementation of said reporter enzyme;

where exposure to the agonist occurs at the same time as, or subsequent to, exposure to the test compound, and wherein decreased reporter enzyme activity after exposure of the

cell to the test compound indicates that the test compound is an antagonist for said GPCR.

19. A method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

a) providing a cell, said cell containing a conjugate comprising a β-arrestin protein as a fusion protein with a reporter enzyme;

b) exposing the cell to a GPCR agonist; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure of the cell to the GPCR agonist indicates that the cell contains a GPCR responsive to said agonist.

20. A method of screening a plurality of cells for those cells which contain a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

a) providing a plurality of cells, said cells containing a conjugate comprising a β-arrestin protein as a fusion protein with a reporter enzyme;

b) exposing the cells to a GPCR agonist; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure to the GPCR agonist indicates β-arrestin protein binding to a GPCR, thereby indicating that the cell contains a GPCR responsive to said GPCR agonist.

21. A method according to Claim 20, wherein the plurality of cells are contained in a tissue.

22. A method according to Claim 20, wherein the plurality of cells are contained in an organ.

23. A method according to Claim 20, wherein step (b) comprises exposing the cells to a plurality of GPCR agonists or ligand libraries.

24. A substrate having deposited thereon a plurality of cells, said cells expressing at least one GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme.

25. A substrate according to Claim 24, wherein the substrate contains an enzyme-labile chemical group which, upon cleavage by the reporter enzyme, releases a product measurable by colorimetry, fluorescence or chemiluminescence.

26. A substrate according to Claim 24, wherein the substrate is made of a material selected from glass, plastic, ceramic, semiconductor, silica, fiber optic, diamond, biocompatible monomer and biocompatible polymer materials.

27. A method of detecting G-protein-coupled receptor (GPCR) pathway activity in a cell expressing at least one GPCR and containing β-arrestin protein as a fusion protein with a reporter enzyme; wherein said enzymatic activity indicates activation of the GPCR pathway.

28. A method according to Claim 27, where the cells are deposited on a substrate prior to detecting said enzymatic activity.

29. A method according to Claim 27, wherein said cell is contained in a tissue.

30. A method according to Claim 27, wherein said cell is contained in an organ.

ABSTRACT

Methods for detecting G-protein coupled receptor (GPCR) activity; methods of assaying GPCR activity; and methods of screening for GPCR ligands, G-protein-coupled receptor kinase (GRK) activity, and compounds that interact with components of the GPRC regulatory process are described.

Cellular Expression of β_2AR-βgal$\Delta\alpha$ Fusion Protein in C2 Clones
(measured by anti-β-gal ELISA)

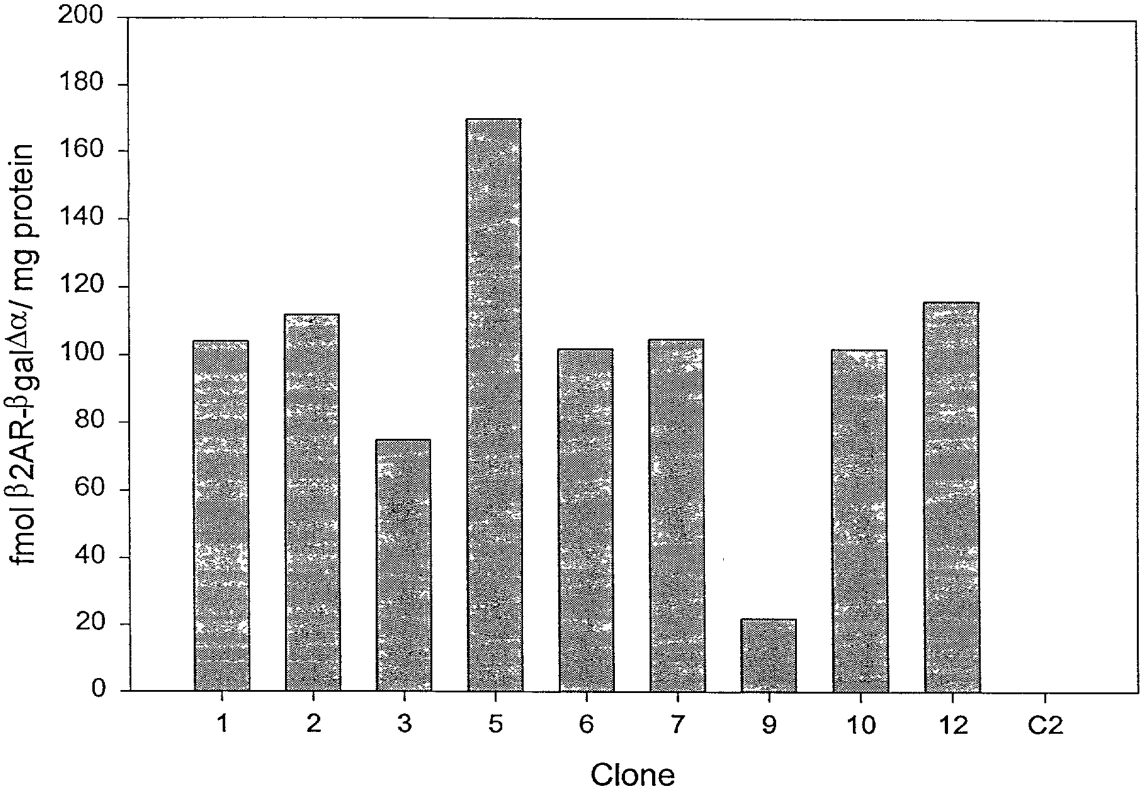

FIGURE 1A

Cellular expression of βArr2-βgalΔω fusion protein in C2 clones
(measured by anti-β gal ELISA)

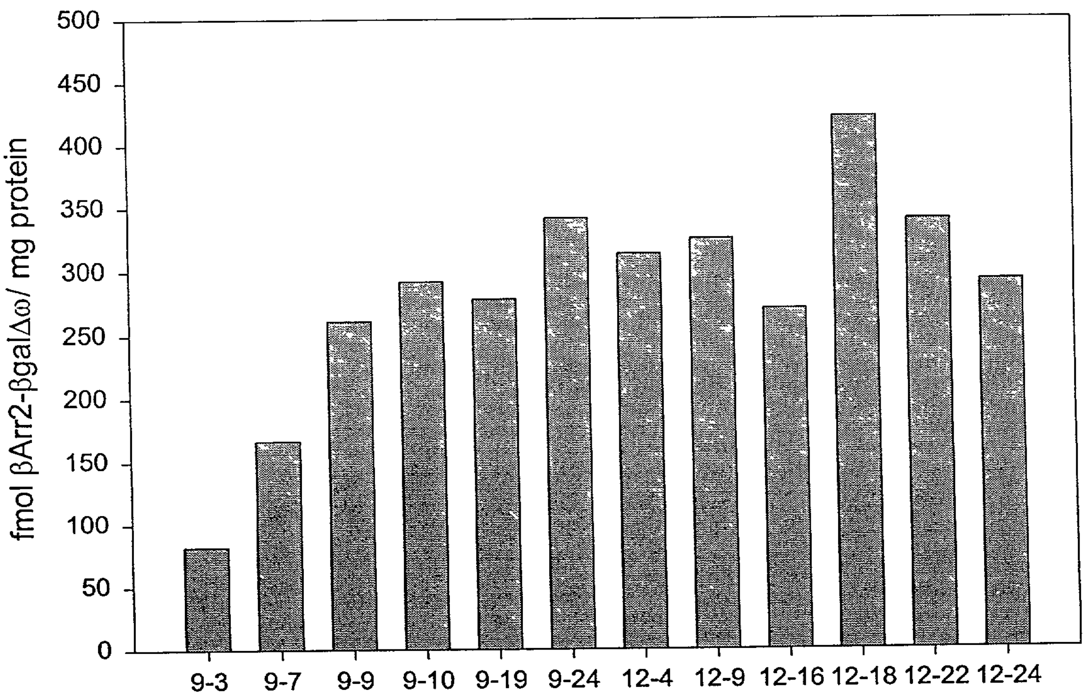

FIGURE 1B

Agonist Stimulated cAMP Response in C2 Cells Expressing β2AR-βgalΔα

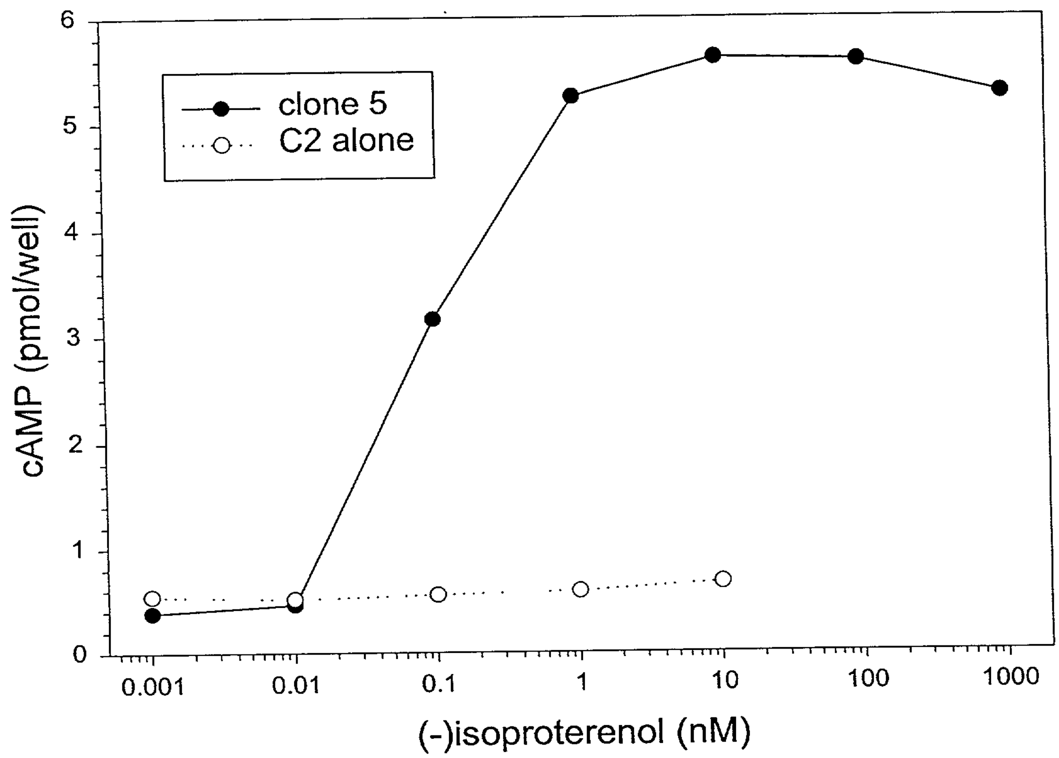

FIGURE 2

β–galactosidase Complementation as a Measurement for β2AR-βgalΔα interacting with βArrestin2-βgalΔω upon agonist Stimulation

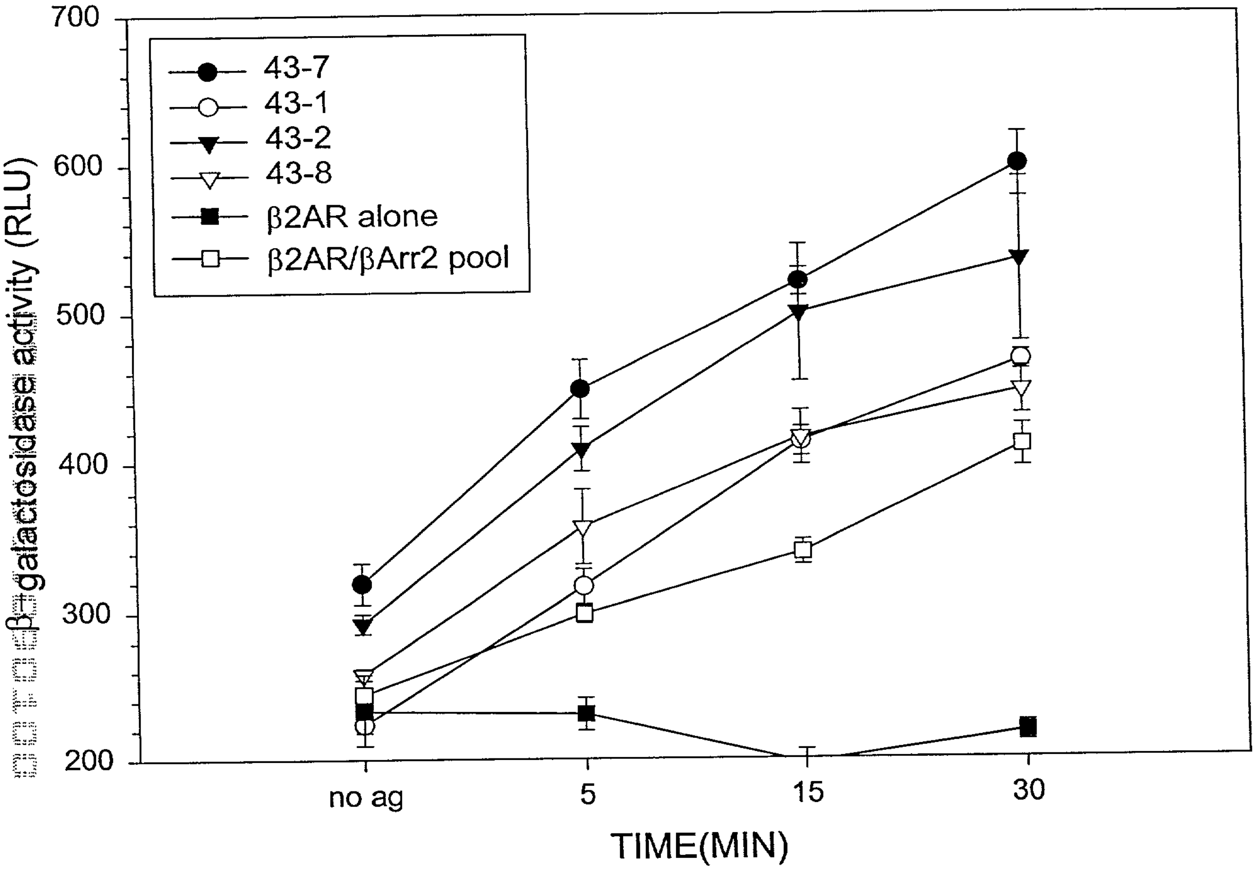

FIGURE 3A

β–galactosidase Complementation as a Measurement for β2AR-βgalΔα Interaction with βArrestin1-βgalΔω upon Agonist Stimulation

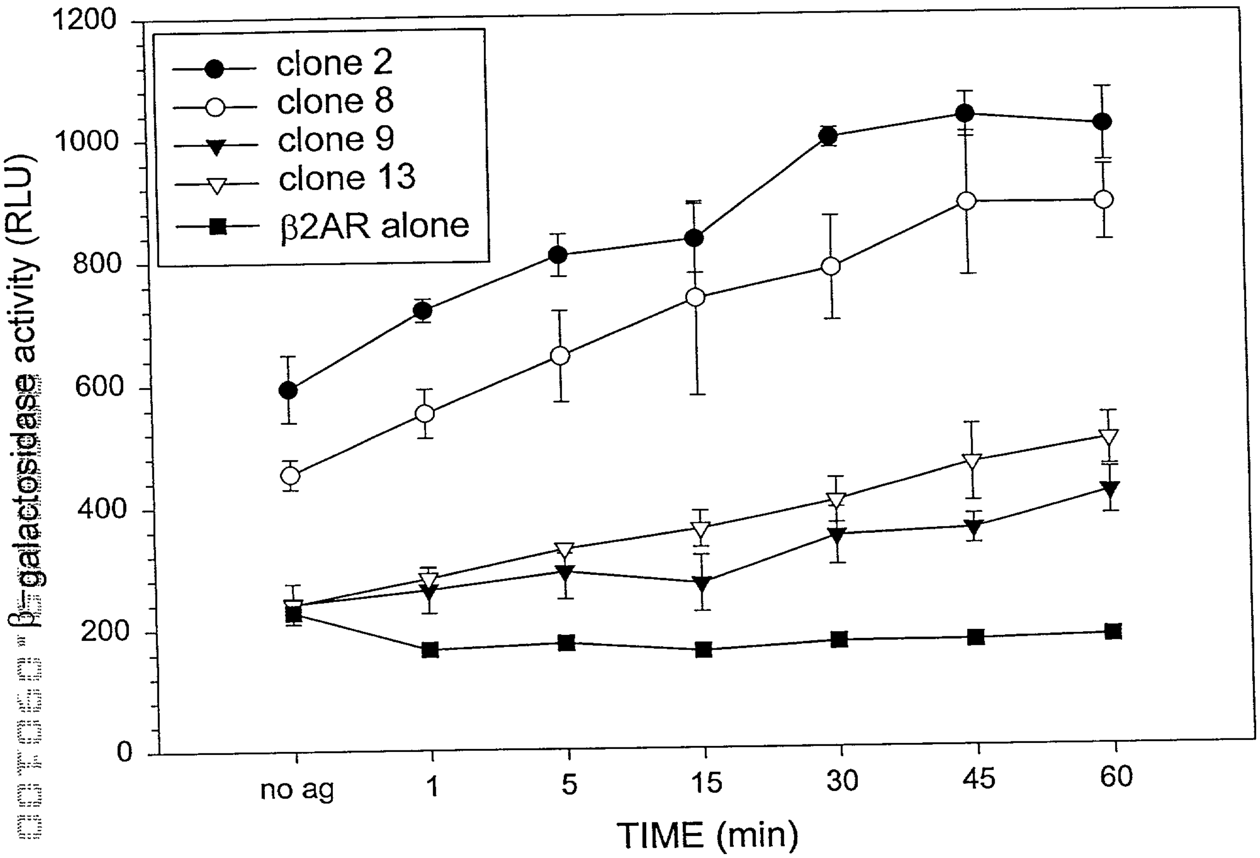

FIGURE 3B

β–galactosidase Activity in Response to Agonist in C2 Cells Coexpressing β2AR-βgalΔα and βArrestin2-βgalΔω Fusion Proteins

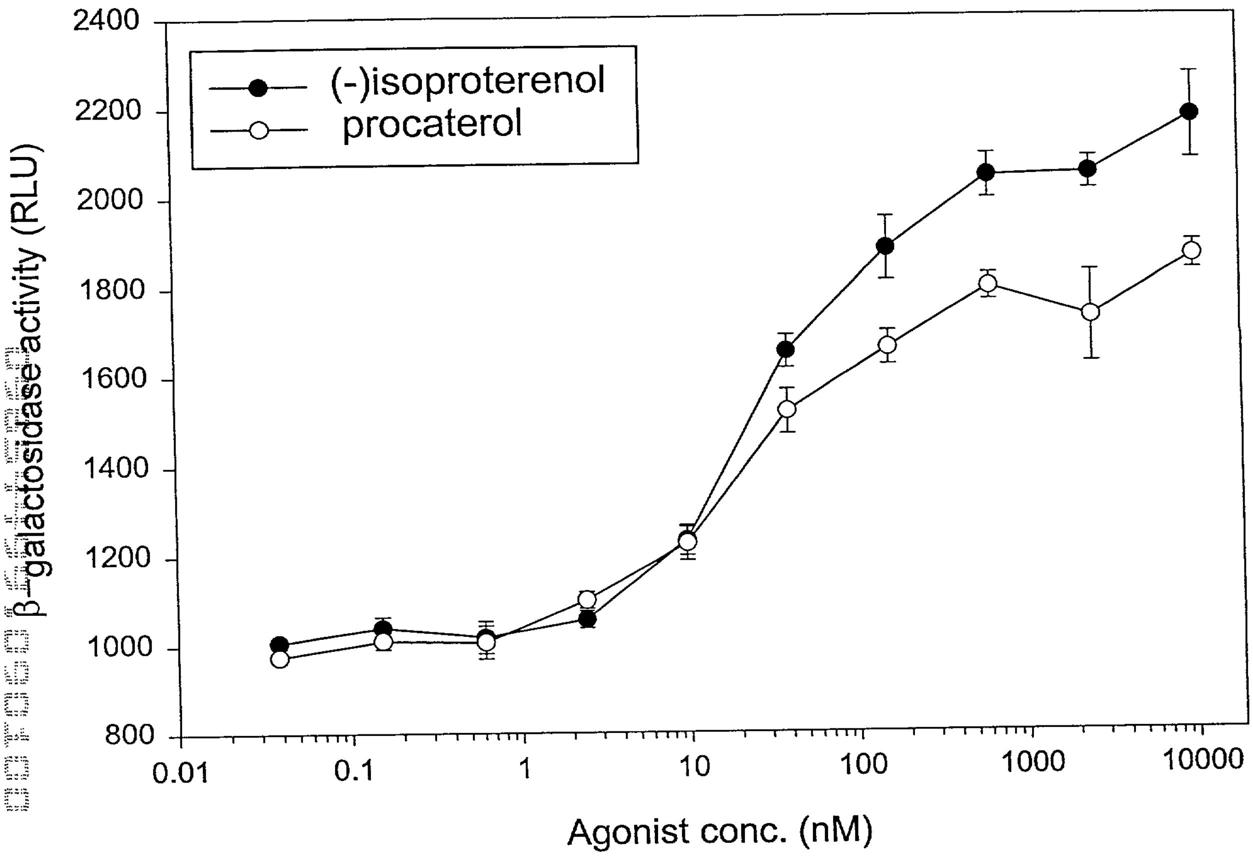

FIGURE 4A

β–galactosidase Activity in Response to Agonist in C2 Cells Coexpressing β2AR-βgalΔα and βArrestin1-βgalΔω Fusion Proteins

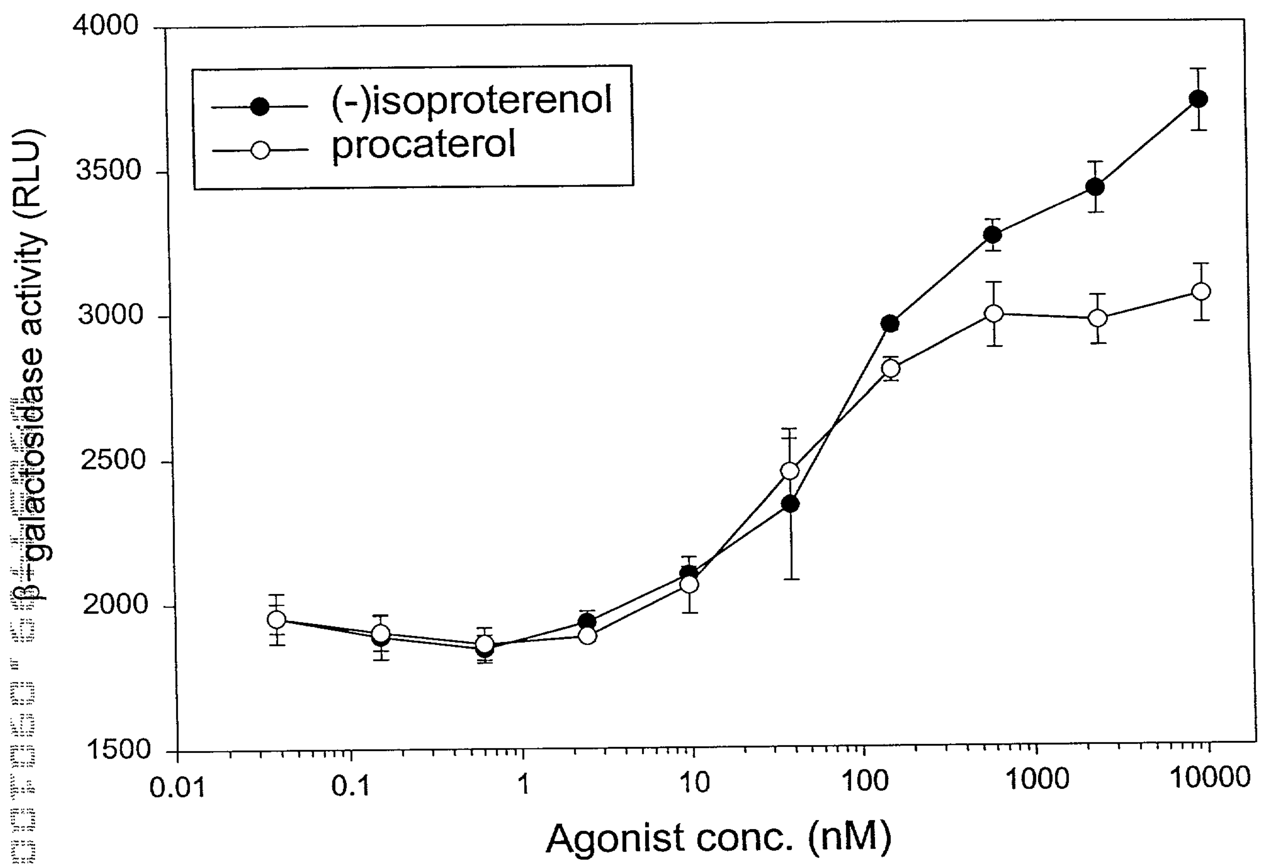

FIGURE 4B

Inhibition of β–galactosidase activity in C2 Cells Coexpressing β2AR–βgalΔα and βArrestin2-βgalΔω Fusion Proteins

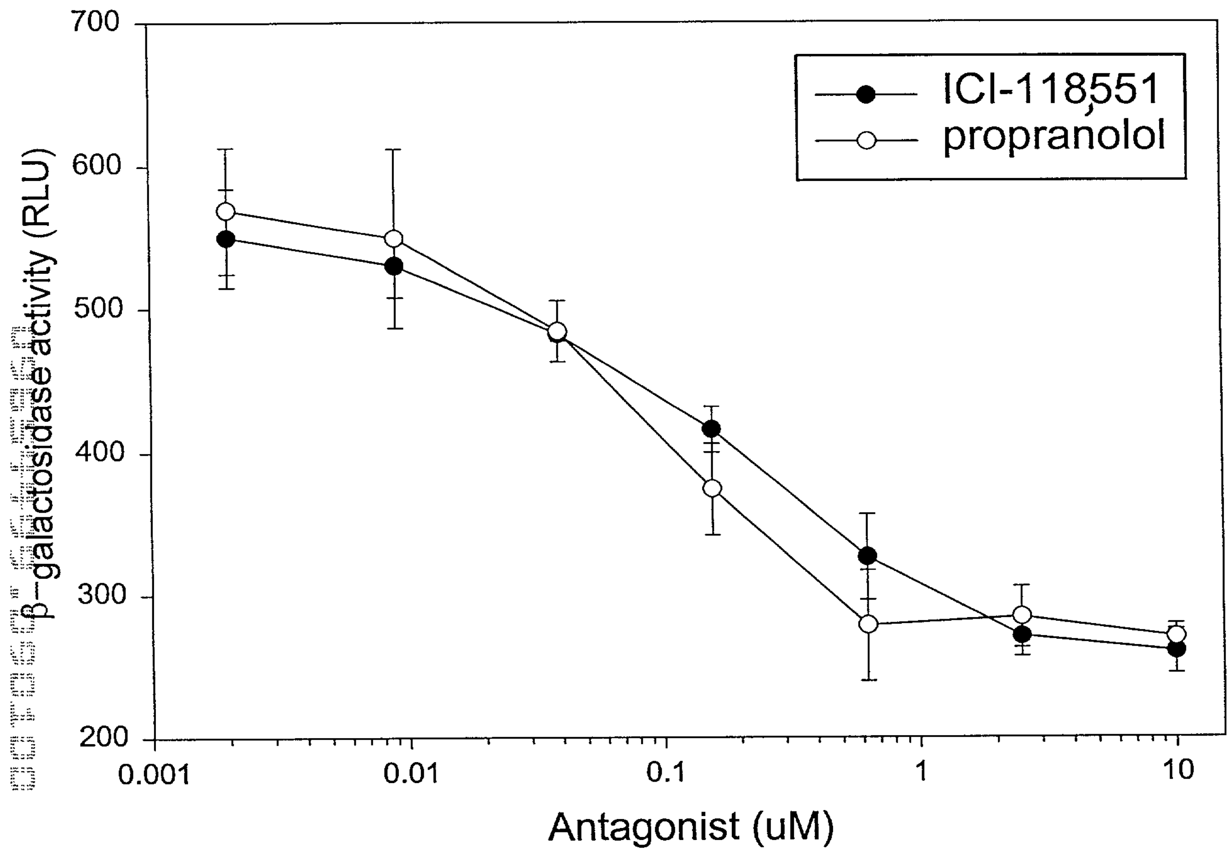

FIGURE 5A

Antagonist Inhibition of β–galactosidase Activity in C2 Cells
Coexpressing β2AR-βgalΔα and βArrestin1-βgalΔω Fusion Proteins

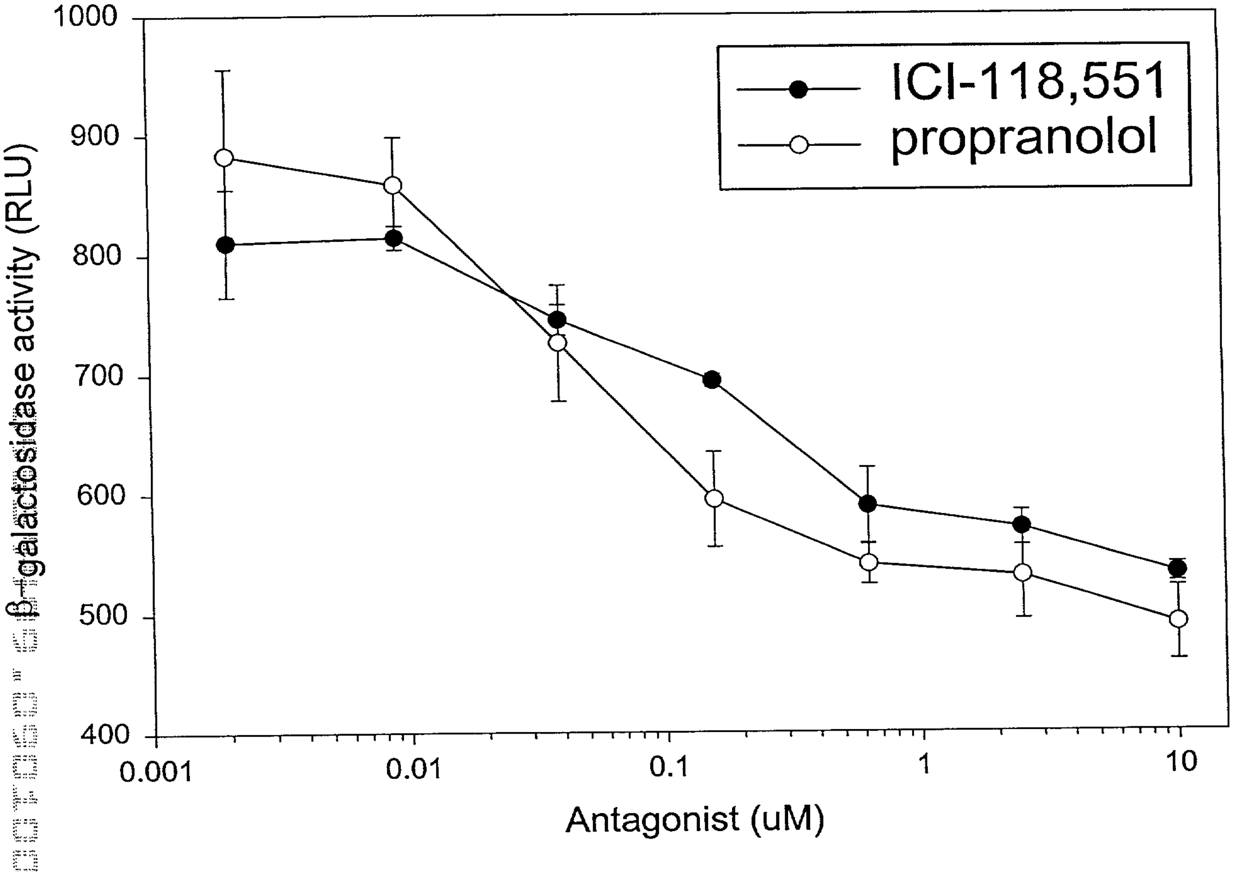

Figure 5B

Agonist Stimulated cAMP Response in Clones or Pools of C2 Cells Coexpressing A2aR-βgalΔα and βArrestin1-βgalΔω Fusion Proteins

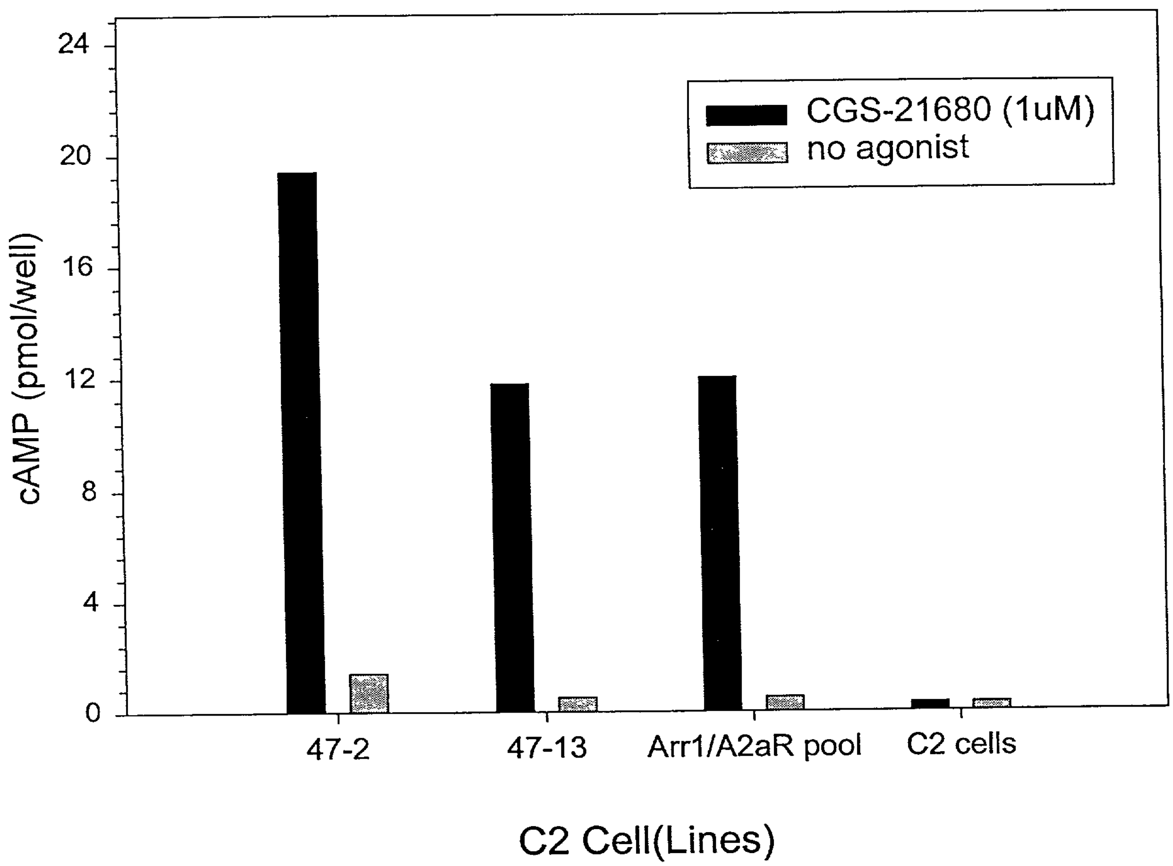

FIGURE 6

Agonist Stimulated cAMP Response in Clones or Pools of C2 Cells Expressing D1-βgalΔα and βArrestin2-βgalΔω Fusion Proteins

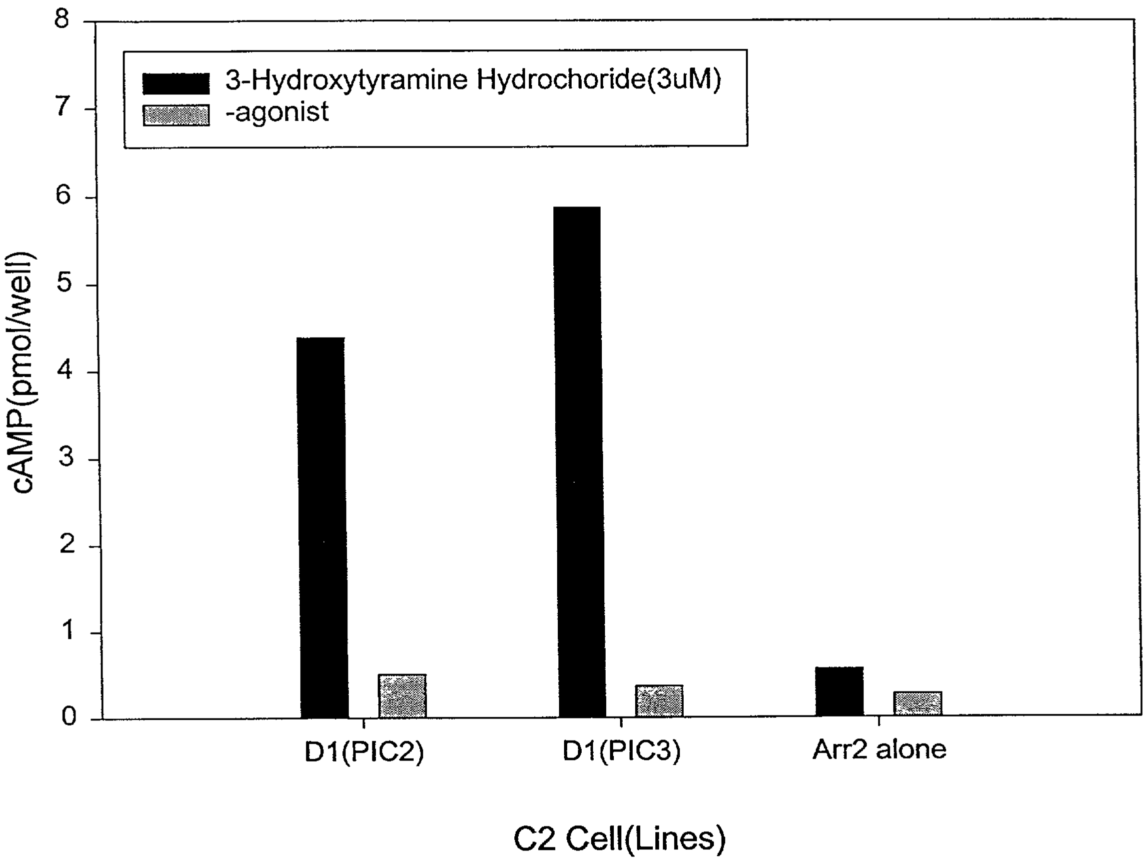

FIGURE 7

β_2AR-βgal$\Delta\omega$ and βarr2-βgal$\Delta\alpha$ Interaction in HEK293 Clones in Response to Isoproterenol Treatment (1 μM)

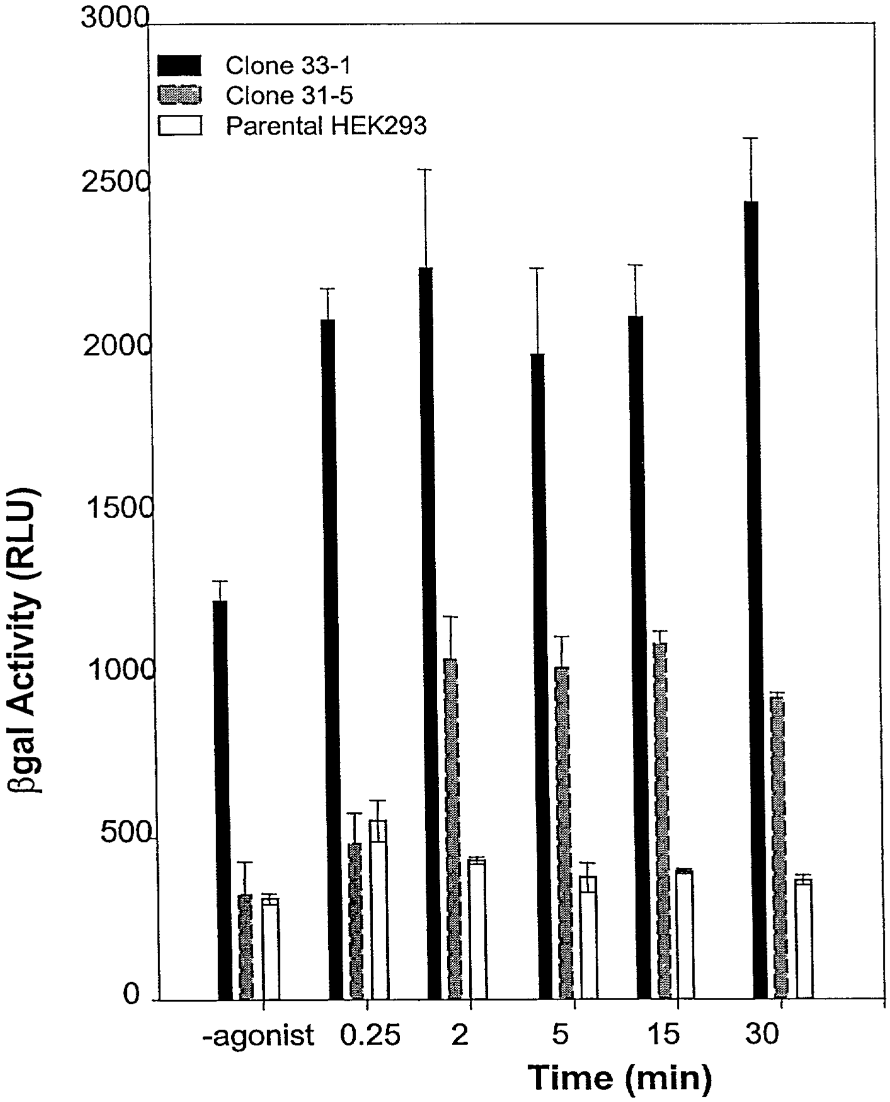

FIGURE 8A

β2AR-βgalΔα and βArr1-βgalΔ Interaction in a CHO Pool in Response to Isoproterenol Treatment(10uM)

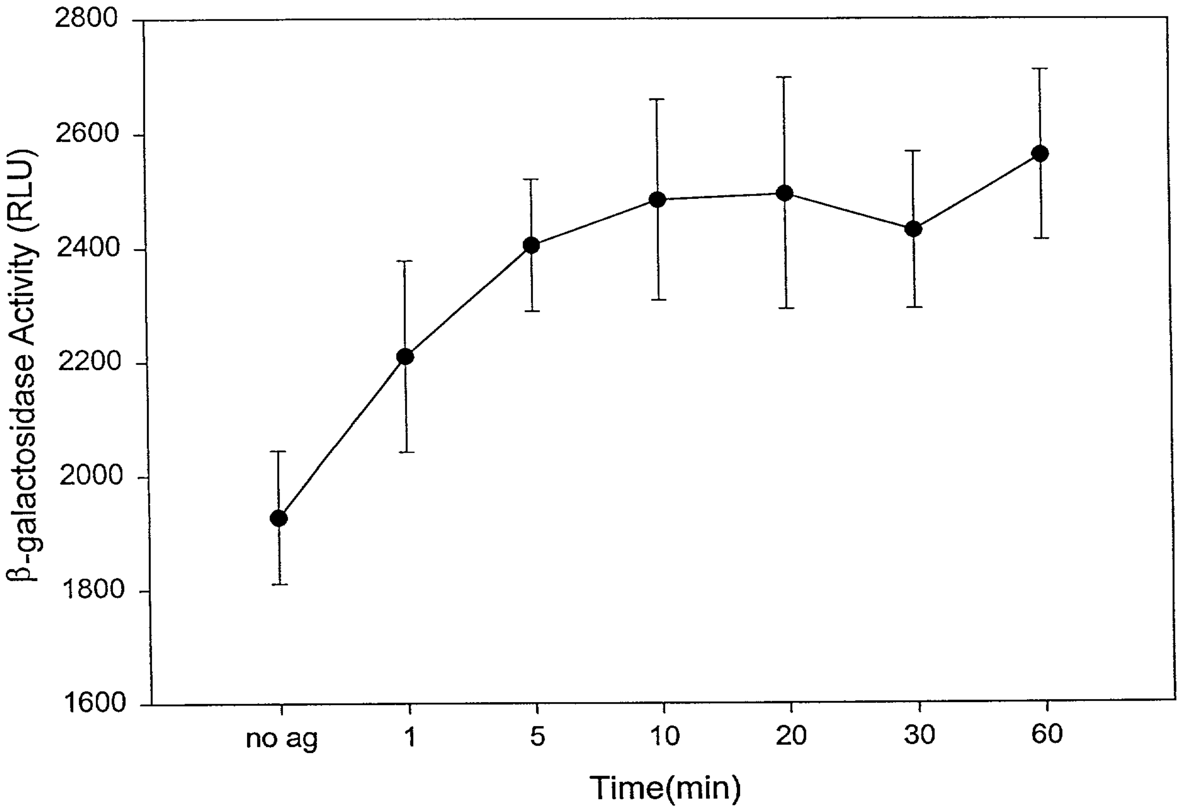

FIGURE 8B

β2AR-βgalΔα and βArr2-βgalΔω Interaction in CHW Clone in Response to Isoproterenol Treatment (10uM)

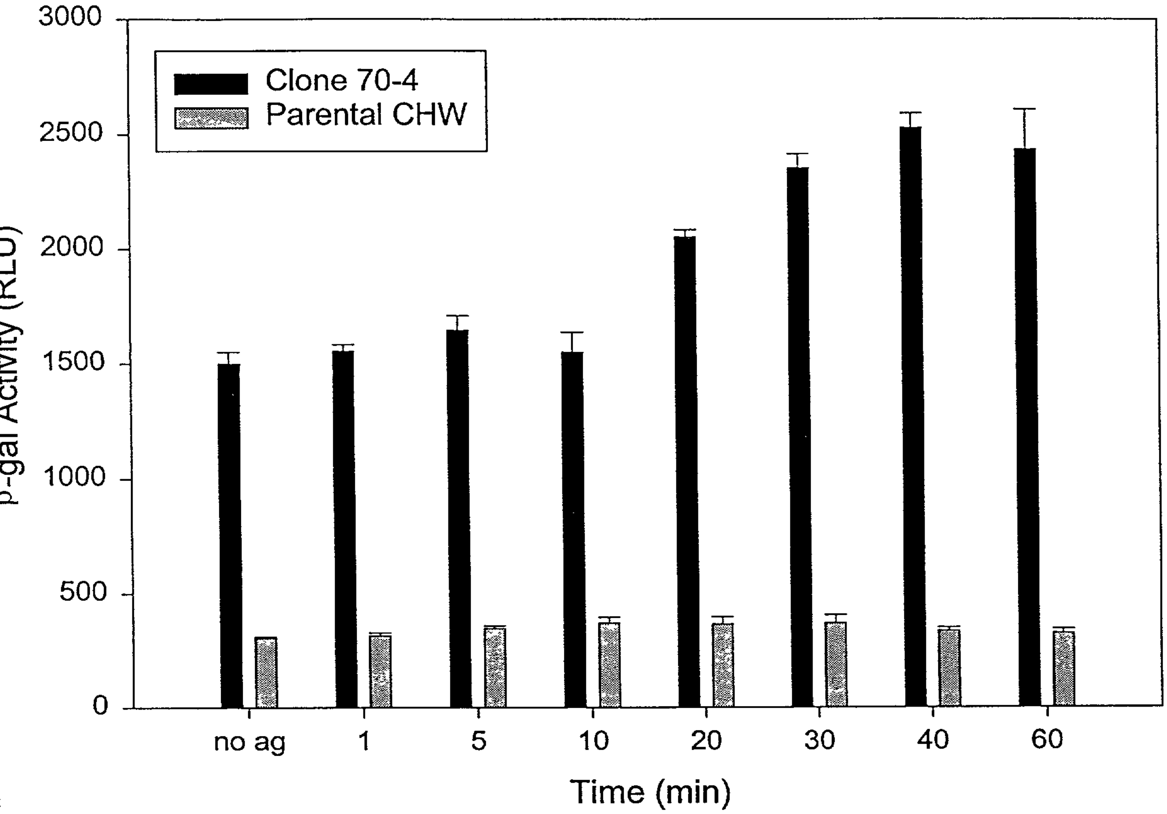

FIGURE 8C

β–galactosidase Complementation as a Measurement for Adrenergic Receptor Homodimerization in HEK 293 Cells Coexpressing β2AR-βgalΔα and β2AR-βgalΔω.

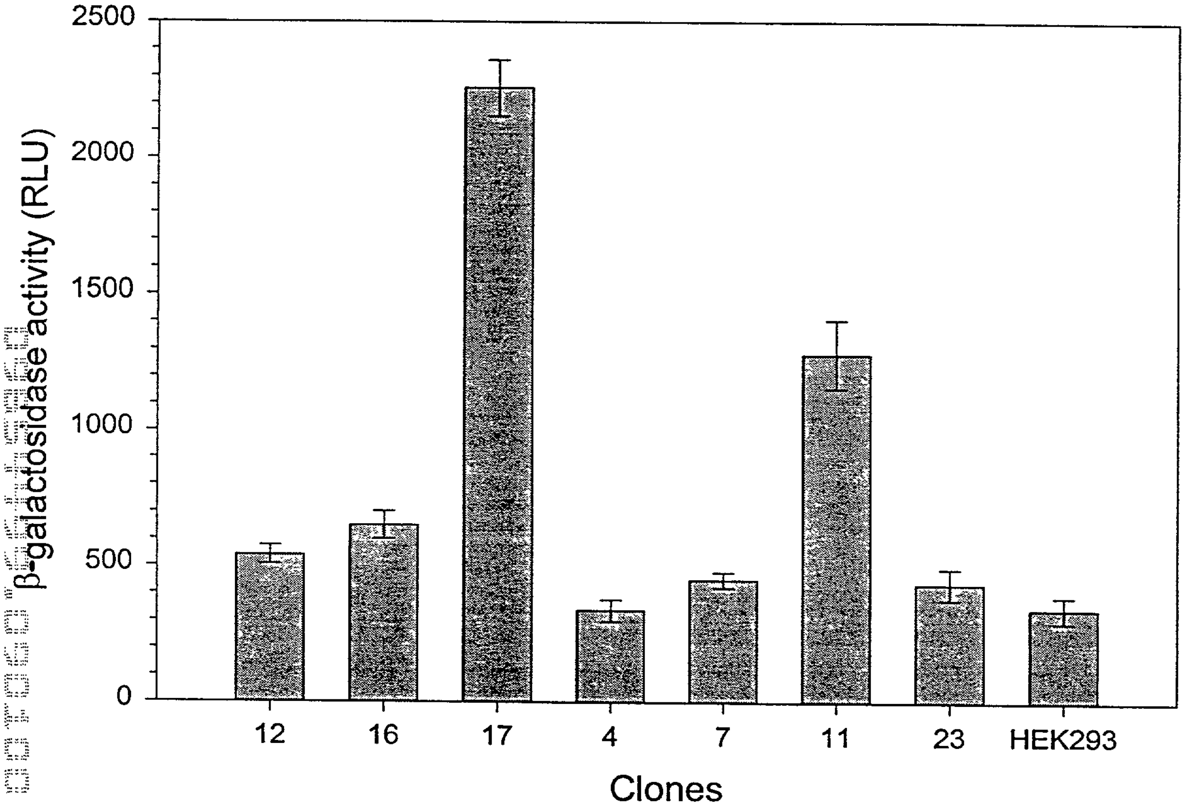

FIGURE 9A

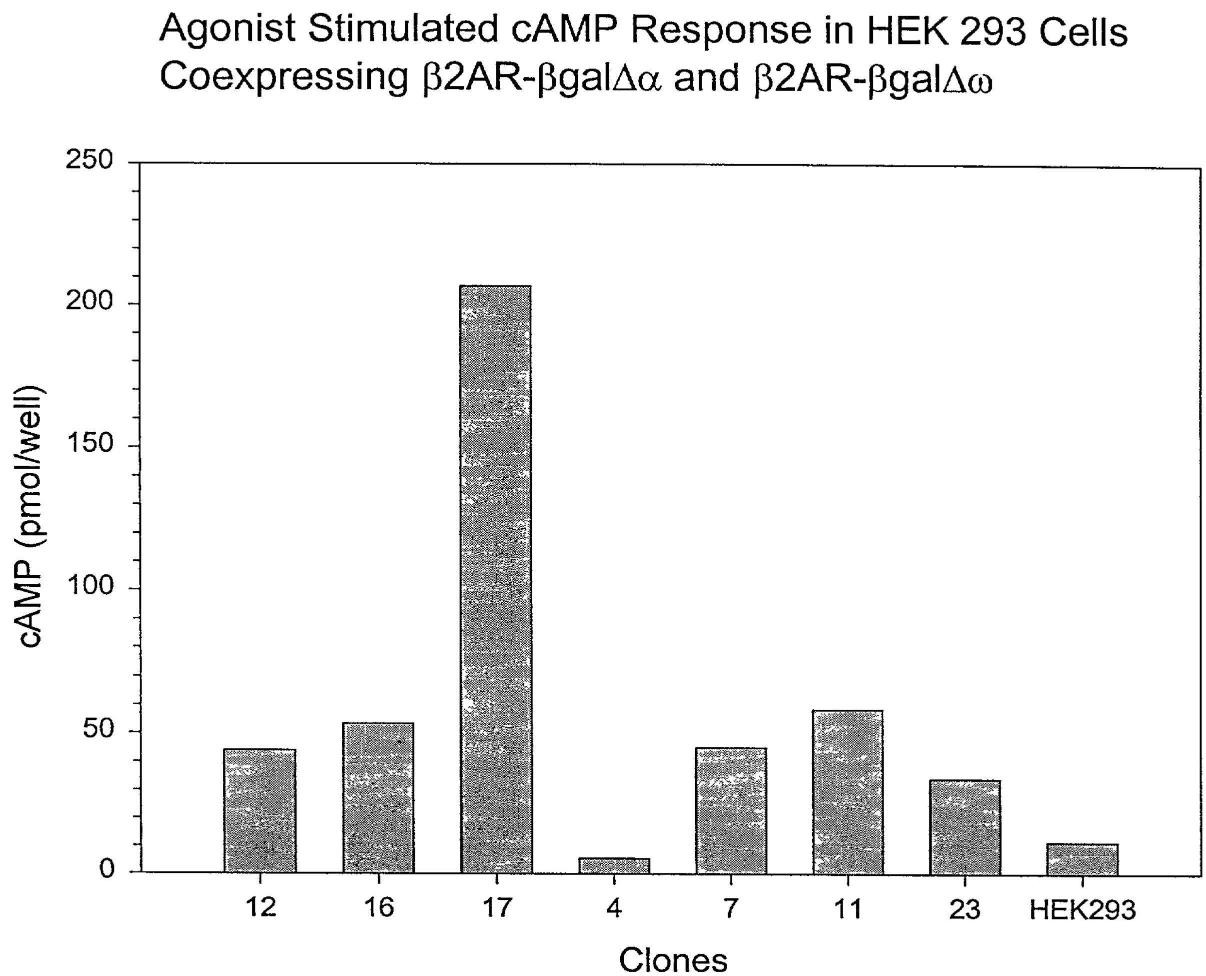
Agonist Stimulated cAMP Response in HEK 293 Cells
Coexpressing β2AR-βgalΔα and β2AR-βgalΔω
cAMP (pmol/well)
250
200
150
100
50
0
12
16
17
4
7
11
23
HEK293
Clones

FIGURE 9B

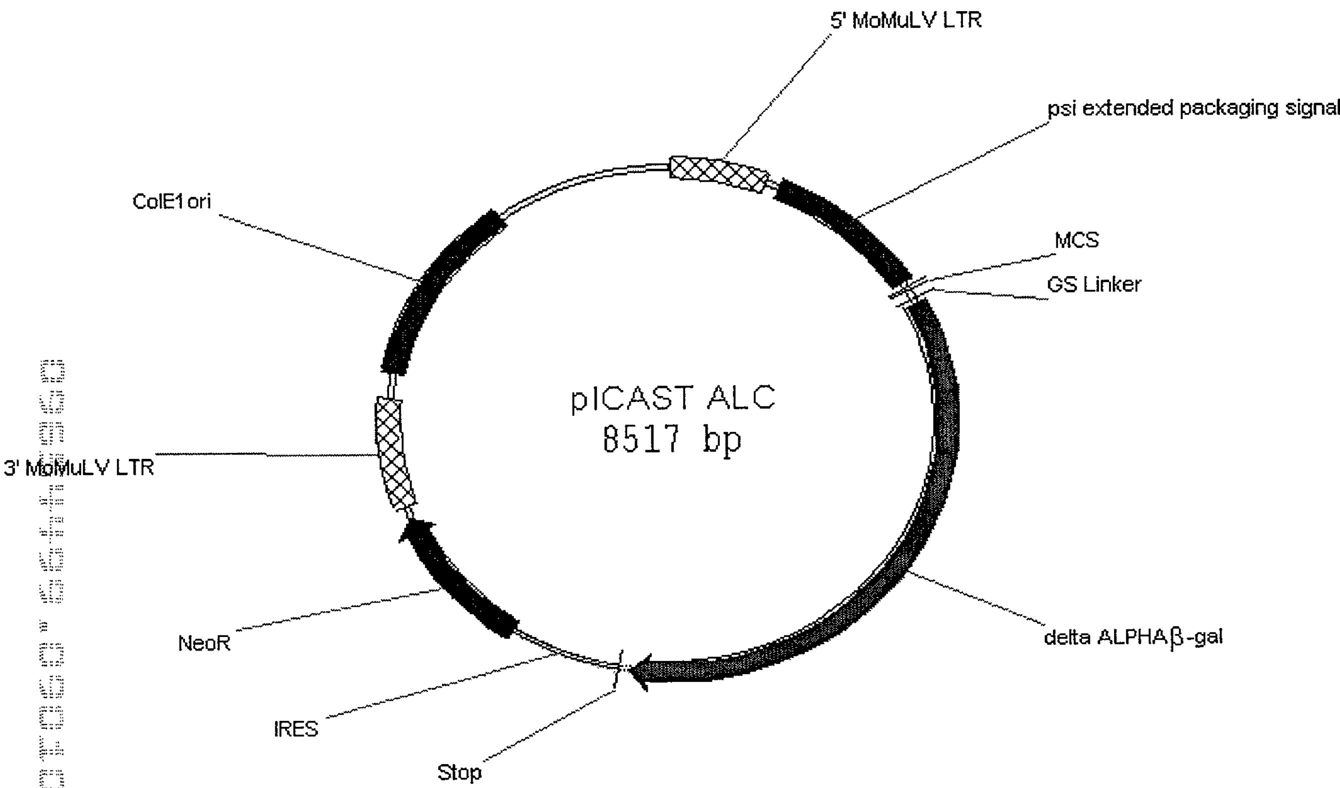
5' MoMuLV LTR
psi extended packaging signal
MCS
GS Linker
pICAST ALC
8517 bp
delta ALPHAβ-gal
Stop
IRES
NeoR
3' MoMuLV LTR
ColE1 ori

Figure 10A

```
1    CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG
     GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC

51   CCCCGGCTCA GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA
     GGGGCCGAGT CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT

101  GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC AAGAACAGAT
     CCTATAGACA CCATTCGTCA AGGACGGGGC CGAGTCCCGG TTCTTGTCTA

151  GGTCCCCAGA TGCGGTCCAG CCCTCAGCAG TTTCTAGAGA ACCATCAGAT
     CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC AAAGATCTCT TGGTAGTCTA

201  GTTTCCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC TTATTTGAAC
     CAAAGGTCCC ACGGGGTTCC TGGACTTTAC TGGGACACGG AATAAACTTG

251  TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA
     ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT

301  GCTCAATAAA AGAGCCCACA ACCCCTCACT CGGGGCGCCA GTCCTCCGAT
     CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA

351  TGACTGAGTC GCCCGGGTAC CCGTGTATCC AATAAACCCT CTTGCAGTTG
     ACTGACTCAG CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC

401  CATCCGACTT GTGGTCTCGC TGTTCCTTGG GAGGGTCTCC TCTGAGTGAT
     GTAGGCTGAA CACCAGAGCG ACAAGGAACC CTCCCAGAGG AGACTCACTA

451  TGACTACCCG TCAGCGGGGG TCTTTCATTT GGGGGCTCGT CCGGGATCGG
     ACTGATGGGC AGTCGCCCCC AGAAAGTAAA CCCCCGAGCA GGCCCTAGCC

501  GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG CAAGCTGGCC
     CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC GTTCGACCGG

551  AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA
     TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGACTAAAAT

601  TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC
     ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG

651  CGTGGTGGAA CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG
     GCACCACCTT GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC

701  TCCCAGGGAC TTTGGGGGCC GTTTTTGTGG CCCGACCTGA GGAAGGGAGT
     AGGGTCCCTG AAACCCCCGG CAAAAACACC GGGCTGGACT CCTTCCCTCA

751  CGATGTGGAA TCCGACCCCG TCAGGATATG TGGTTCTGGT AGGAGACGAG
     GCTACACCTT AGGCTGGGGC AGTCCTATAC ACCAAGACCA TCCTCTGCTC

801  AACCTAAAAC AGTTCCCGCC TCCGTCTGAA TTTTTGCTTT CGGTTTGGAA
     TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA GCCAAACCTT

851  CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT
     GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA

901  CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC
     GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG
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FIGURE 10B

```
 951  TCCCTTAAGT TTGACCTTAG GTAACTGGAA AGATGTCGAG CGGCTCGCTC
      AGGGAATTCA AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG
---------------------------------------------------------------------------
1001  ACAACCAGTC GGTAGATGTC AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT
      TGTTGGTCAG CCATCTACAG TTCTTCTCTG CAACCCAATG GAAGACGAGA
---------------------------------------------------------------------------
1051  GCAGAATGGC CAACCTTTAA CGTCGGATGG CCGCGAGACG GCACCTTTAA
      CGTCTTACCG GTTGGAAATT GCAGCCTACC GGCGCTCTGC CGTGGAAATT
---------------------------------------------------------------------------
1101  CCGAGACCTC ATCACCCAGG TTAAGATCAA GGTCTTTTCA CCTGGCCCGC
      GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT GGACCGGGCG
---------------------------------------------------------------------------
1151  ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT
      TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA
---------------------------------------------------------------------------
1201  TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC
      AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG
---------------------------------------------------------------------------
1251  TCCTCTTCCT CCATCCGCCC CGTCTCTCCC CCTTGAACCT CCTCGTTCGA
      AGGAGAAGGA GGTAGGCGGG GCAGAGAGGG GGAACTTGGA GGAGCAAGCT
---------------------------------------------------------------------------
1301  CCCCGCCTCG ATCCTCCCTT TATCCAGCCC TCACTCCTTC TCTAGGCGCC
      GGGGCGGAGC TAGGAGGGAA ATAGGTCGGG AGTGAGGAAG AGATCCGCGG
---------------------------------------------------------------------------
1351  GGCCGCTCTA GCCCATTAAT ACGACTCACT ATAGGGCGAT TCGAATCAGG
      CCGGCGAGAT CGGGTAATTA TGCTGAGTGA TATCCCGCTA AGCTTAGTCC
---------------------------------------------------------------------------
1401  CCTTGGCGCG CCGGATCCTT AATTAAGCGC AATTGGGAGG TGGCGGTAGC
      GGAACCGCGC GGCCTAGGAA TTAATTCGCG TTAACCCTCC ACCGCCATCG
---------------------------------------------------------------------------
  +2          M  G   V  I  T   D  S  L   A  V  V  A   R  T  D
             ]---------------------------------------------
1451  CTCGAGATGG GCGTGATTAC GGATTCACTG GCCGTCGTGG CCCGCACCGA
      GAGCTCTACC CGCACTAATG CCTAAGTGAC CGGCAGCACC GGGCGTGGCT
---------------------------------------------------------------------------
  +2   R  P  S   Q  Q  L  R   S  L  N   G  E  W   R  F  A
      ----------------------------------------------------
1501  TCGCCCTTCC CAACAGTTAC GCAGCCTGAA TGGCGAATGG CGCTTTGCCT
      AGCGGGAAGG GTTGTCAATG CGTCGGACTT ACCGCTTACC GCGAAACGGA
---------------------------------------------------------------------------
  +2 W  F  P  A   P  E  A   V  P  E  S   W  L  E   C  D  L
      ----------------------------------------------------
1551  GGTTTCCGGC ACCAGAAGCG GTGCCGGAAA GCTGGCTGGA GTGCGATCTT
      CCAAAGGCCG TGGTCTTCGC CACGGCCTTT CGACCGACCT CACGCTAGAA
---------------------------------------------------------------------------
  +2  P  E  A  D   T  V  V   V  P  S   N  W  Q  M   H  G  Y
      ----------------------------------------------------
1601  CCTGAGGCCG ATACTGTCGT CGTCCCCTCA AACTGGCAGA TGCACGGTTA
      GGACTCCGGC TATGACAGCA GCAGGGGAGT TTGACCGTCT ACGTGCCAAT
---------------------------------------------------------------------------
  +2   D  A  P   I  Y  T  N   V  T  Y   P  I  T   V  N  P
      ----------------------------------------------------
1651  CGATGCGCCC ATCTACACCA ACGTGACCTA TCCCATTACG GTCAATCCGC
      GCTACGCGGG TAGATGTGGT TGCACTGGAT AGGGTAATGC CAGTTAGGCG
---------------------------------------------------------------------------
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+2   P  F  V  P   T  E  N   P  T  G  C   Y  S  L   T  F  N
     ---------------------------------------------------------
1701 CGTTTGTTCC CACGGAGAAT CCGACGGGTT GTTACTCGCT CACATTTAAT
     GCAAACAAGG GTGCCTCTTA GGCTGCCCAA CAATGAGCGA GTGTAAATTA
-----------------------------------------------------------------------
+2   V  D  E  S   W  L  Q   E  G  Q   T  R  I  I   F  D  G
     ---------------------------------------------------------
1751 GTTGATGAAA GCTGGCTACA GGAAGGCCAG ACGCGAATTA TTTTTGATGG
     CAACTACTTT CGACCGATGT CCTTCCGGTC TGCGCTTAAT AAAAACTACC
-----------------------------------------------------------------------
+2    V  N  S   A  F  H  L   W  C  N   G  R  W   V  G  Y
     ---------------------------------------------------------
1801 CGTTAACTCG GCGTTTCATC TGTGGTGCAA CGGGCGCTGG GTCGGTTACG
     GCAATTGAGC CGCAAAGTAG ACACCACGTT GCCCGCGACC CAGCCAATGC
-----------------------------------------------------------------------
+2   G  Q  D  S   R  L  P   S  E  F  D   L  S  A   F  L  R
     ---------------------------------------------------------
1851 GCCAGGACAG TCGTTTGCCG TCTGAATTTG ACCTGAGCGC ATTTTTACGC
     CGGTCCTGTC AGCAAACGGC AGACTTAAAC TGGACTCGCG TAAAAATGCG
-----------------------------------------------------------------------
+2    A  G  E  N   R  L  A   V  M  V   L  R  W  S   D  G  S
     ---------------------------------------------------------
1901 GCCGGAGAAA ACCGCCTCGC GGTGATGGTG CTGCGCTGGA GTGACGGCAG
     CGGCCTCTTT TGGCGGAGCG CCACTACCAC GACGCGACCT CACTGCCGTC
-----------------------------------------------------------------------
+2    Y  L  E   D  Q  D  M   W  R  M   S  G  I   F  R  D
     ---------------------------------------------------------
1951 TTATCTGGAA GATCAGGATA TGTGGCGGAT GAGCGGCATT TTCCGTGACG
     AATAGACCTT CTAGTCCTAT ACACCGCCTA CTCGCCGTAA AAGGCACTGC
-----------------------------------------------------------------------
+2   V  S  L  L   H  K  P   T  T  Q  I   S  D  F   H  V  A
     ---------------------------------------------------------
2001 TCTCGTTGCT GCATAAACCG ACTACACAAA TCAGCGATTT CCATGTTGCC
     AGAGCAACGA CGTATTTGGC TGATGTGTTT AGTCGCTAAA GGTACAACGG
-----------------------------------------------------------------------
+2    T  R  F  N   D  D  F   S  R  A   V  L  E  A   E  V  Q
     ---------------------------------------------------------
2051 ACTCGCTTTA ATGATGATTT CAGCCGCGCT GTACTGGAGG CTGAAGTTCA
     TGAGCGAAAT TACTACTAAA GTCGGCGCGA CATGACCTCC GACTTCAAGT
-----------------------------------------------------------------------
+2    M  C  G   E  L  R  D   Y  L  R   V  T  V   S  L  W
     ---------------------------------------------------------
2101 GATGTGCGGC GAGTTGCGTG ACTACCTACG GGTAACAGTT TCTTTATGGC
     CTACACGCCG CTCAACGCAC TGATGGATGC CCATTGTCAA AGAAATACCG
-----------------------------------------------------------------------
+2   Q  G  E  T   Q  V  A   S  G  T  A   P  F  G   G  E  I
     ---------------------------------------------------------
2151 AGGGTGAAAC GCAGGTCGCC AGCGGCACCG CGCCTTTCGG CGGTGAAATT
     TCCCACTTTG CGTCCAGCGG TCGCCGTGGC GCGGAAAGCC GCCACTTTAA
-----------------------------------------------------------------------
+2    I  D  E  R   G  G  Y   A  D  R   V  T  L  R   L  N  V
     ---------------------------------------------------------
2201 ATCGATGAGC GTGGTGGTTA TGCCGATCGC GTCACACTAC GTCTGAACGT
     TAGCTACTCG CACCACCAAT ACGGCTAGCG CAGTGTGATG CAGACTTGCA
-----------------------------------------------------------------------
+2    E  N  P   K  L  W  S   A  E  I   P  N  L   Y  R  A
     ---------------------------------------------------------
2251 CGAAAACCCG AAACTGTGGA GCGCCGAAAT CCCGAATCTC TATCGTGCGG
     GCTTTTGGGC TTTGACACCT CGCGGCTTTA GGGCTTAGAG ATAGCACGCC
-----------------------------------------------------------------------
```

```
  +2 V  V  E  L   H  T  A   D  G  T  L   I  E  A   E  A  C
     ----------------------------------------------------------
2301 TGGTTGAACT GCACACCGCC GACGGCACGC TGATTGAAGC AGAAGCCTGC
     ACCAACTTGA CGTGTGGCGG CTGCCGTGCG ACTAACTTCG TCTTCGGACG
----------------------------------------------------------------------------------------------
  +2  D  V  G  F   R  E  V   R  I  E   N  G  L  L   L  L  N
     ----------------------------------------------------------
2351 GATGTCGGTT TCCGCGAGGT GCGGATTGAA AATGGTCTGC TGCTGCTGAA
     CTACAGCCAA AGGCGCTCCA CGCCTAACTT TTACCAGACG ACGACGACTT
----------------------------------------------------------------------------------------------
  +2   G  K  P   L  L  I  R   G  V  N   R  H  E   H  H  P
     ----------------------------------------------------------
2401 CGGCAAGCCG TTGCTGATTC GAGGCGTTAA CCGTCACGAG CATCATCCTC
     GCCGTTCGGC AACGACTAAG CTCCGCAATT GGCAGTGCTC GTAGTAGGAG
----------------------------------------------------------------------------------------------
  +2 L  H  G  Q   V  M  D   E  Q  T  M   V  Q  D   I  L  L
     ----------------------------------------------------------
2451 TGCATGGTCA GGTCATGGAT GAGCAGACGA TGGTGCAGGA TATCCTGCTG
     ACGTACCAGT CCAGTACCTA CTCGTCTGCT ACCACGTCCT ATAGGACGAC
----------------------------------------------------------------------------------------------
  +2  M  K  Q  N   N  F  N   A  V  R   C  S  H  Y   P  N  H
     ----------------------------------------------------------
2501 ATGAAGCAGA ACAACTTTAA CGCCGTGCGC TGTTCGCATT ATCCGAACCA
     TACTTCGTCT TGTTGAAATT GCGGCACGCG ACAAGCGTAA TAGGCTTGGT
----------------------------------------------------------------------------------------------
  +2   P  L  W   Y  T  L  C   D  R  Y   G  L  Y   V  V  D
     ----------------------------------------------------------
2551 TCCGCTGTGG TACACGCTGT GCGACCGCTA CGGCCTGTAT GTGGTGGATG
     AGGCGACACC ATGTGCGACA CGCTGGCGAT GCCGGACATA CACCACCTAC
----------------------------------------------------------------------------------------------
  +2 E  A  N  I   E  T  H   G  M  V  P   M  N  R   L  T  D
     ----------------------------------------------------------
2601 AAGCCAATAT TGAAACCCAC GGCATGGTGC CAATGAATCG TCTGACCGAT
     TTCGGTTATA ACTTTGGGTG CCGTACCACG GTTACTTAGC AGACTGGCTA
----------------------------------------------------------------------------------------------
  +2  D  P  R  W   L  P  A   M  S  E   R  V  T  R   M  V  Q
     ----------------------------------------------------------
2651 GATCCGCGCT GGCTACCGGC GATGAGCGAA CGCGTAACGC GAATGGTGCA
     CTAGGCGCGA CCGATGGCCG CTACTCGCTT GCGCATTGCG CTTACCACGT
----------------------------------------------------------------------------------------------
  +2  R  D  R   N  H  P  S   V  I  I   W  S  L   G  N  E
     ----------------------------------------------------------
2701 GCGCGATCGT AATCACCCGA GTGTGATCAT CTGGTCGCTG GGGAATGAAT
     CGCGCTAGCA TTAGTGGGCT CACACTAGTA GACCAGCGAC CCCTTACTTA
----------------------------------------------------------------------------------------------
  +2 S  G  H  G   A  N  H   D  A  L  Y   R  W  I   K  S  V
     ----------------------------------------------------------
2751 CAGGCCACGG CGCTAATCAC GACGCGCTGT ATCGCTGGAT CAAATCTGTC
     GTCCGGTGCC GCGATTAGTG CTGCGCGACA TAGCGACCTA GTTTAGACAG
----------------------------------------------------------------------------------------------
  +2  D  P  S  R   P  V  Q   Y  E  G   G  G  A  D   T  T  A
     ----------------------------------------------------------
2801 GATCCTTCCC GCCCGGTGCA GTATGAAGGC GGCGGAGCCG ACACCACGGC
     CTAGGAAGGG CGGGCCACGT CATACTTCCG CCGCCTCGGC TGTGGTGCCG
----------------------------------------------------------------------------------------------
  +2   T  D  I   I  C  P  M   Y  A  R   V  D  E   D  Q  P
     ----------------------------------------------------------
2851 CACCGATATT ATTTGCCCGA TGTACGCGCG CGTGGATGAA GACCAGCCCT
     GTGGCTATAA TAAACGGGCT ACATGCGCGC GCACCTACTT CTGGTCGGGA
----------------------------------------------------------------------------------------------
```

```
  +2 F  P  A  V   P  K  W   S  I  K  K   W  L  S   L  P  G
     ------------------------------------------------------
2901 TCCCGGCTGT GCCGAAATGG TCCATCAAAA AATGGCTTTC GCTACCTGGA
     AGGGCCGACA CGGCTTTACC AGGTAGTTTT TTACCGAAAG CGATGGACCT
-----------------------------------------------------------
  +2  E  T  R  P   L  I  L   C  E  Y   A  H  A  M   G  N  S
     ------------------------------------------------------
2951 GAGACGCGCC CGCTGATCCT TTGCGAATAC GCCCACGCGA TGGGTAACAG
     CTCTGCGCGG GCGACTAGGA AACGCTTATG CGGGTGCGCT ACCCATTGTC
-----------------------------------------------------------
  +2  L  G  G   F  A  K  Y   W  Q  A   F  R  Q   Y  P  R
     ------------------------------------------------------
3001 TCTTGGCGGT TTCGCTAAAT ACTGGCAGGC GTTTCGTCAG TATCCCCGTT
     AGAACCGCCA AAGCGATTTA TGACCGTCCG CAAAGCAGTC ATAGGGGCAA
-----------------------------------------------------------
  +2 L  Q  G  G   F  V  W   D  W  V  D   Q  S  L   I  K  Y
     ------------------------------------------------------
3051 TACAGGGCGG CTTCGTCTGG GACTGGGTGG ATCAGTCGCT GATTAAATAT
     ATGTCCCGCC GAAGCAGACC CTGACCCACC TAGTCAGCGA CTAATTTATA
-----------------------------------------------------------
  +2  D  E  N  G   N  P  W   S  A  Y   G  G  D  F   G  D  T
     ------------------------------------------------------
3101 GATGAAAACG GCAACCCGTG GTCGGCTTAC GGCGGTGATT TTGGCGATAC
     CTACTTTTGC CGTTGGGCAC CAGCCGAATG CCGCCACTAA AACCGCTATG
-----------------------------------------------------------
  +2  P  N  D   R  Q  F  C   M  N  G   L  V  F   A  D  R
     ------------------------------------------------------
3151 GCCGAACGAT CGCCAGTTCT GTATGAACGG TCTGGTCTTT GCCGACCGCA
     CGGCTTGCTA GCGGTCAAGA CATACTTGCC AGACCAGAAA CGGCTGGCGT
-----------------------------------------------------------
  +2 T  P  H  P   A  L  T   E  A  K  H   Q  Q  Q   F  F  Q
     ------------------------------------------------------
3201 CGCCGCATCC AGCGCTGACG GAAGCAAAAC ACCAGCAGCA GTTTTTCCAG
     GCGGCGTAGG TCGCGACTGC CTTCGTTTTG TGGTCGTCGT CAAAAAGGTC
-----------------------------------------------------------
  +2  F  R  L  S   G  Q  T   I  E  V   T  S  E  Y   L  F  R
     ------------------------------------------------------
3251 TTCCGTTTAT CCGGGCAAAC CATCGAAGTG ACCAGCGAAT ACCTGTTCCG
     AAGGCAAATA GGCCCGTTTG GTAGCTTCAC TGGTCGCTTA TGGACAAGGC
-----------------------------------------------------------
  +2  H  S  D   N  E  L  L   H  W  M   V  A  L   D  G  K
     ------------------------------------------------------
3301 TCATAGCGAT AACGAGCTCC TGCACTGGAT GGTGGCGCTG GATGGTAAGC
     AGTATCGCTA TTGCTCGAGG ACGTGACCTA CCACCGCGAC CTACCATTCG
-----------------------------------------------------------
  +2 P  L  A  S   G  E  V   P  L  D  V   A  P  Q   G  K  Q
     ------------------------------------------------------
3351 CGCTGGCAAG CGGTGAAGTG CCTCTGGATG TCGCTCCACA AGGTAAACAG
     GCGACCGTTC GCCACTTCAC GGAGACCTAC AGCGAGGTGT TCCATTTGTC
-----------------------------------------------------------
  +2  L  I  E  L   P  E  L   P  Q  P   E  S  A  G   Q  L  W
     ------------------------------------------------------
3401 TTGATTGAAC TGCCTGAACT ACCGCAGCCG GAGAGCGCCG GGCAACTCTG
     AACTAACTTG ACGGACTTGA TGGCGTCGGC CTCTCGCGGC CCGTTGAGAC
-----------------------------------------------------------
  +2  L  T  V   R  V  V  Q   P  N  A   T  A  W   S  E  A
     ------------------------------------------------------
3451 GCTCACAGTA CGCGTAGTGC AACCGAACGC GACCGCATGG TCAGAAGCCG
     CGAGTGTCAT GCGCATCACG TTGGCTTGCG CTGGCGTACC AGTCTTCGGC
-----------------------------------------------------------
```

```
  +2 G  H  I  S   A  W  Q   Q  W  R  L   A  E  N   L  S  V
     ---------------------------------------------------------
3501 GGCACATCAG CGCCTGGCAG CAGTGGCGTC TGGCGGAAAA CCTCAGTGTG
     CCGTGTAGTC GCGGACCGTC GTCACCGCAG ACCGCCTTTT GGAGTCACAC
------------------------------------------------------------------------------------------
  +2  T  L  P  A   A  S  H   A  I  P   H  L  T  T   S  E  M
     ---------------------------------------------------------
3551 ACGCTCCCCG CCGCGTCCCA CGCCATCCCG CATCTGACCA CCAGCGAAAT
     TGCGAGGGGC GGCGCAGGGT GCGGTAGGGC GTAGACTGGT GGTCGCTTTA
------------------------------------------------------------------------------------------
  +2   D  F  C   I  E  L  G   N  K  R   W  Q  F   N  R  Q
     ---------------------------------------------------------
3601 GGATTTTTGC ATCGAGCTGG GTAATAAGCG TTGGCAATTT AACCGCCAGT
     CCTAAAAACG TAGCTCGACC CATTATTCGC AACCGTTAAA TTGGCGGTCA
------------------------------------------------------------------------------------------
  +2 S  G  F  L   S  Q  M   W  I  G  D   K  K  Q   L  L  T
     ---------------------------------------------------------
3651 CAGGCTTTCT TTCACAGATG TGGATTGGCG ATAAAAAACA ACTGCTGACG
     GTCCGAAAGA AAGTGTCTAC ACCTAACCGC TATTTTTTGT TGACGACTGC
------------------------------------------------------------------------------------------
  +2  P  L  R  D   Q  F  T   R  A  P   L  D  N  D   I  G  V
     ---------------------------------------------------------
3701 CCGCTGCGCG ATCAGTTCAC CCGTGCACCG CTGGATAACG ACATTGGCGT
     GGCGACGCGC TAGTCAAGTG GGCACGTGGC GACCTATTGC TGTAACCGCA
------------------------------------------------------------------------------------------
  +2   S  E  A   T  R  I  D   P  N  A   W  V  E   R  W  K
     ---------------------------------------------------------
3751 AAGTGAAGCG ACCCGCATTG ACCCTAACGC CTGGGTCGAA CGCTGGAAGG
     TTCACTTCGC TGGGCGTAAC TGGGATTGCG GACCCAGCTT GCGACCTTCC
------------------------------------------------------------------------------------------
  +2 A  A  G  H   Y  Q  A   E  A  A  L   L  Q  C   T  A  D
     ---------------------------------------------------------
3801 CGGCGGGCCA TTACCAGGCC GAAGCAGCGT TGTTGCAGTG CACGGCAGAT
     GCCGCCCGGT AATGGTCCGG CTTCGTCGCA ACAACGTCAC GTGCCGTCTA
------------------------------------------------------------------------------------------
  +2  T  L  A  D   A  V  L   I  T  T   A  H  A  W   Q  H  Q
     ---------------------------------------------------------
3851 ACACTTGCTG ATGCGGTGCT GATTACGACC GCTCACGCGT GGCAGCATCA
     TGTGAACGAC TACGCCACGA CTAATGCTGG CGAGTGCGCA CCGTCGTAGT
------------------------------------------------------------------------------------------
  +2  G  K  T   L  F  I  S   R  K  T   Y  R  I   D  G  S
     ---------------------------------------------------------
3901 GGGGAAAACC TTATTTATCA GCCGGAAAAC CTACCGGATT GATGGTAGTG
     CCCCTTTTGG AATAAATAGT CGGCCTTTTG GATGGCCTAA CTACCATCAC
------------------------------------------------------------------------------------------
  +2 G  Q  M  A   I  T  V   D  V  E  V   A  S  D   T  P  H
     ---------------------------------------------------------
3951 GTCAAATGGC GATTACCGTT GATGTTGAAG TGGCGAGCGA TACACCGCAT
     CAGTTTACCG CTAATGGCAA CTACAACTTC ACCGCTCGCT ATGTGGCGTA
------------------------------------------------------------------------------------------
  +2  P  A  R  I   G  L  N   C  Q  L   A  Q  V  A   E  R  V
     ---------------------------------------------------------
4001 CCGGCGCGGA TTGGCCTGAA CTGCCAGCTG GCGCAGGTAG CAGAGCGGGT
     GGCCGCGCCT AACCGGACTT GACGGTCGAC CGCGTCCATC GTCTCGCCCA
------------------------------------------------------------------------------------------
  +2   N  W  L   G  L  G  P   Q  E  N   Y  P  D   R  L  T
     ---------------------------------------------------------
4051 AAACTGGCTC GGATTAGGGC CGCAAGAAAA CTATCCCGAC CGCCTTACTG
     TTTGACCGAG CCTAATCCCG GCGTTCTTTT GATAGGGCTG GCGGAATGAC
------------------------------------------------------------------------------------------
```

```
 +2 A  A  C  F   D  R  W   D  L  P  L   S  D  M   Y  T  P
    ---------------------------------------------------
4101 CCGCCTGTTT TGACCGCTGG GATCTGCCAT TGTCAGACAT GTATACCCCG
     GGCGGACAAA ACTGGCGACC CTAGACGGTA ACAGTCTGTA CATATGGGGC
---------------------------------------------------------------------------
 +2  Y  V  F  P   S  E  N   G  L  R   C  G  T  R   E  L  N
    ---------------------------------------------------
4151 TACGTCTTCC CGAGCGAAAA CGGTCTGCGC TGCGGGACGC GCGAATTGAA
     ATGCAGAAGG GCTCGCTTTT GCCAGACGCG ACGCCCTGCG CGCTTAACTT
---------------------------------------------------------------------------
 +2   Y  G  P   H  Q  W  R   G  D  F   Q  F  N   I  S  R
    ---------------------------------------------------
4201 TTATGGCCCA CACCAGTGGC GCGGCGACTT CCAGTTCAAC ATCAGCCGCT
     AATACCGGGT GTGGTCACCG CGCCGCTGAA GGTCAAGTTG TAGTCGGCGA
---------------------------------------------------------------------------
 +2 Y  S  Q  Q   Q  L  M   E  T  S  H   R  H  L   L  H  A
    ---------------------------------------------------
4251 ACAGTCAACA GCAACTGATG GAAACCAGCC ATCGCCATCT GCTGCACGCG
     TGTCAGTTGT CGTTGACTAC CTTTGGTCGG TAGCGGTAGA CGACGTGCGC
---------------------------------------------------------------------------
 +2  E  E  G  T   W  L  N   I  D  G   F  H  M  G   I  G  G
    ---------------------------------------------------
4301 GAAGAAGGCA CATGGCTGAA TATCGACGGT TTCCATATGG GGATTGGTGG
     CTTCTTCCGT GTACCGACTT ATAGCTGCCA AAGGTATACC CCTAACCACC
---------------------------------------------------------------------------
 +2   D  D  S   W  S  P  S   V  S  A   E  F  Q   L  S  A
    ---------------------------------------------------
4351 CGACGACTCC TGGAGCCCGT CAGTATCGGC GGAATTCCAG CTGAGCGCCG
     GCTGCTGAGG ACCTCGGGCA GTCATAGCCG CCTTAAGGTC GACTCGCGGC
---------------------------------------------------------------------------
 +2 G  R  Y  H   Y  Q  L   V  W  C  Q   K  R  S   D  Y  K
    ---------------------------------------------------
4401 GTCGCTACCA TTACCAGTTG GTCTGGTGTC AAAAAAGATC TGACTATAAA
     CAGCGATGGT AATGGTCAAC CAGACCACAG TTTTTTCTAG ACTGATATTT
---------------------------------------------------------------------------
 +2  D  E  D  L   D  H  H   H  H  H   H  R
    ------------------------------------->
4451 GATGAGGACC TCGACCATCA TCATCATCAT CACCGGTAAT AATAGGTAGA
     CTACTCCTGG AGCTGGTAGT AGTAGTAGTA GTGGCCATTA TTATCCATCT
---------------------------------------------------------------------------
4501 TAAGTGACTG ATTAGATGCA TTGATCCCTC GACCAATTCC GGTTATTTTC
     ATTCACTGAC TAATCTACGT AACTAGGGAG CTGGTTAAGG CCAATAAAAG
---------------------------------------------------------------------------
4551 CACCATATTG CCGTCTTTTG GCAATGTGAG GGCCCGGAAA CCTGGCCCTG
     GTGGTATAAC GGCAGAAAAC CGTTACACTC CCGGGCCTTT GGACCGGGAC
---------------------------------------------------------------------------
4601 TCTTCTTGAC GAGCATTCCT AGGGGTCTTT CCCCTCTCGC CAAAGGAATG
     AGAAGAACTG CTCGTAAGGA TCCCCAGAAA GGGGAGAGCG GTTTCCTTAC
---------------------------------------------------------------------------
4651 CAAGGTCTGT TGAATGTCGT GAAGGAAGCA GTTCCTCTGG AAGCTTCTTG
     GTTCCAGACA ACTTACAGCA CTTCCTTCGT CAAGGAGACC TTCGAAGAAC
---------------------------------------------------------------------------
4701 AAGACAAACA ACGTCTGTAG CGACCCTTTG CAGGCAGCGG AACCCCCCAC
     TTCTGTTTGT TGCAGACATC GCTGGGAAAC GTCCGTCGCC TTGGGGGGTG
---------------------------------------------------------------------------
4751 CTGGCGACAG GTGCCTCTGC GGCCAAAAGC CACGTGTATA AGATACACCT
     GACCGCTGTC CACGGAGACG CCGGTTTTCG GTGCACATAT TCTATGTGGA
---------------------------------------------------------------------------
```

```
4801  GCAAAGGCGG CACAACCCCA GTGCCACGTT GTGAGTTGGA TAGTTGTGGA
      CGTTTCCGCC GTGTTGGGGT CACGGTGCAA CACTCAACCT ATCAACACCT

4851  AAGAGTCAAA TGGCTCTCCT CAAGCGTATT CAACAAGGGG CTGAAGGATG
      TTCTCAGTTT ACCGAGAGGA GTTCGCATAA GTTGTTCCCC GACTTCCTAC

4901  CCCAGAAGGT ACCCCATTGT ATGGGATCTG ATCTGGGGCC TCGGTGCACA
      GGGTCTTCCA TGGGGTAACA TACCCTAGAC TAGACCCCGG AGCCACGTGT

4951  TGCTTTACAT GTGTTTAGTC GAGGTTAAAA AACGTCTAGG CCCCCCGAAC
      ACGAAATGTA CACAAATCAG CTCCAATTTT TTGCAGATCC GGGGGGCTTG

5001  CACGGGGACG TGGTTTTCCT TTGAAAAACA CGATGATAAT ACCATGATTG
      GTGCCCCTGC ACCAAAAGGA AACTTTTTGT GCTACTATTA TGGTACTAAC

5051  AACAAGATGG ATTGCACGCA GGTTCTCCGG CCGCTTGGGT GGAGAGGCTA
      TTGTTCTACC TAACGTGCGT CCAAGAGGCC GGCGAACCCA CCTCTCCGAT

5101  TTCGGCTATG ACTGGGCACA ACAGACAATC GGCTGCTCTG ATGCCGCCGT
      AAGCCGATAC TGACCCGTGT TGTCTGTTAG CCGACGAGAC TACGGCGGCA

5151  GTTCCGGCTG TCAGCGCAGG GGCGCCCGGT TCTTTTTGTC AAGACCGACC
      CAAGGCCGAC AGTCGCGTCC CCGCGGGCCA AGAAAAACAG TTCTGGCTGG

5201  TGTCCGGTGC CCTGAATGAA CTGCAGGACG AGGCAGCGCG GCTATCGTGG
      ACAGGCCACG GGACTTACTT GACGTCCTGC TCCGTCGCGC CGATAGCACC

5251  CTGGCCACGA CGGGCGTTCC TTGCGCAGCT GTGCTCGACG TTGTCACTGA
      GACCGGTGCT GCCCGCAAGG AACGCGTCGA CACGAGCTGC AACAGTGACT

5301  AGCGGGAAGG GACTGGCTGC TATTGGGCGA AGTGCCGGGG CAGGATCTCC
      TCGCCCTTCC CTGACCGACG ATAACCCGCT TCACGGCCCC GTCCTAGAGG

5351  TGTCATCTCA CCTTGCTCCT GCCGAGAAAG TATCCATCAT GGCTGATGCA
      ACAGTAGAGT GGAACGAGGA CGGCTCTTTC ATAGGTAGTA CCGACTACGT

5401  ATGCGGCGGC TGCATACGCT TGATCCGGCT ACCTGCCCAT TCGACCACCA
      TACGCCGCCG ACGTATGCGA ACTAGGCCGA TGGACGGGTA AGCTGGTGGT

5451  AGCGAAACAT CGCATCGAGC GAGCACGTAC TCGGATGGAA GCCGGTCTTG
      TCGCTTTGTA GCGTAGCTCG CTCGTGCATG AGCCTACCTT CGGCCAGAAC

5501  TCGATCAGGA TGATCTGGAC GAAGAGCATC AGGGGCTCGC GCCAGCCGAA
      AGCTAGTCCT ACTAGACCTG CTTCTCGTAG TCCCCGAGCG CGGTCGGCTT

5551  CTGTTCGCCA GGCTCAAGGC GCGCATGCCC GACGGCGAGG ATCTCGTCGT
      GACAAGCGGT CCGAGTTCCG CGCGTACGGG CTGCCGCTCC TAGAGCAGCA

5601  GACCCATGGC GATGCCTGCT TGCCGAATAT CATGGTGGAA AATGGCCGCT
      CTGGGTACCG CTACGGACGA ACGGCTTATA GTACCACCTT TTACCGGCGA

5651  TTTCTGGATT CATCGACTGT GGCCGGCTGG GTGTGGCGGA CCGCTATCAG
      AAAGACCTAA GTAGCTGACA CCGGCCGACC CACACCGCCT GGCGATAGTC

5701  GACATAGCGT TGGCTACCCG TGATATTGCT GAAGAGCTTG GCGGCGAATG
      CTGTATCGCA ACCGATGGGC ACTATAACGA CTTCTCGAAC CGCCGCTTAC
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5751  GGCTGACCGC TTCCTCGTGC TTTACGGTAT CGCCGCTCCC GATTCGCAGC
      CCGACTGGCG AAGGAGCACG AAATGCCATA GCGGCGAGGG CTAAGCGTCG
--------------------------------------------------------------------------
5801  GCATCGCCTT CTATCGCCTT CTTGACGAGT TCTTCTGAGC GGGACTCTGG
      CGTAGCGGAA GATAGCGGAA GAACTGCTCA AGAAGACTCG CCCTGAGACC
--------------------------------------------------------------------------
5851  GGTTCGCATC GATAAAATAA AAGATTTTAT TTAGTCTCCA GAAAAAGGGG
      CCAAGCGTAG CTATTTTATT TTCTAAAATA AATCAGAGGT CTTTTTCCCC
--------------------------------------------------------------------------
5901  GGAATGAAAG ACCCCACCTG TAGGTTTGGC AAGCTAGCTT AAGTAACGCC
      CCTTACTTTC TGGGGTGGAC ATCCAAACCG TTCGATCGAA TTCATTGCGG
--------------------------------------------------------------------------
5951  ATTTTGCAAG GCATGGAAAA ATACATAACT GAGAATAGAG AAGTTCAGAT
      TAAAACGTTC CGTACCTTTT TATGTATTGA CTCTTATCTC TTCAAGTCTA
--------------------------------------------------------------------------
6001  CAAGGTCAGG AACAGATGGA ACAGCTGAAT ATGGGCCAAA CAGGATATCT
      GTTCCAGTCC TTGTCTACCT TGTCGACTTA TACCCGGTTT GTCCTATAGA
--------------------------------------------------------------------------
6051  GTGGTAAGCA GTTCCTGCCC CGGCTCAGGG CCAAGAACAG ATGGAACAGC
      CACCATTCGT CAAGGACGGG GCCGAGTCCC GGTTCTTGTC TACCTTGTCG
--------------------------------------------------------------------------
6101  TGAATATGGG CCAAACAGGA TATCTGTGGT AAGCAGTTCC TGCCCCGGCT
      ACTTATACCC GGTTTGTCCT ATAGACACCA TTCGTCAAGG ACGGGGCCGA
--------------------------------------------------------------------------
6151  CAGGGCCAAG AACAGATGGT CCCCAGATGC GGTCCAGCCC TCAGCAGTTT
      GTCCCGGTTC TTGTCTACCA GGGGTCTACG CCAGGTCGGG AGTCGTCAAA
--------------------------------------------------------------------------
6201  CTAGAGAACC ATCAGATGTT TCCAGGGTGC CCCAAGGACC TGAAATGACC
      GATCTCTTGG TAGTCTACAA AGGTCCCACG GGGTTCCTGG ACTTTACTGG
--------------------------------------------------------------------------
6251  CTGTGCCTTA TTTGAACTAA CCAATCAGTT CGCTTCTCGC TTCTGTTCGC
      GACACGGAAT AAACTTGATT GGTTAGTCAA GCGAAGAGCG AAGACAAGCG
--------------------------------------------------------------------------
6301  GCGCTTCTGC TCCCCGAGCT CAATAAAAGA GCCCACAACC CCTCACTCGG
      CGCGAAGACG AGGGGCTCGA GTTATTTTCT CGGGTGTTGG GGAGTGAGCC
--------------------------------------------------------------------------
6351  GGCGCCAGTC CTCCGATTGA CTGAGTCGCC CGGGTACCCG TGTATCCAAT
      CCGCGGTCAG GAGGCTAACT GACTCAGCGG GCCCATGGGC ACATAGGTTA
--------------------------------------------------------------------------
6401  AAACCCTCTT GCAGTTGCAT CCGACTTGTG GTCTCGCTGT TCCTTGGGAG
      TTTGGGAGAA CGTCAACGTA GGCTGAACAC CAGAGCGACA AGGAACCCTC
--------------------------------------------------------------------------
6451  GGTCTCCTCT GAGTGATTGA CTACCCGTCA GCGGGGGTCT TTCATTCATG
      CCAGAGGAGA CTCACTAACT GATGGGCAGT CGCCCCCAGA AAGTAAGTAC
--------------------------------------------------------------------------
6501  CAGCATGTAT CAAAATTAAT TTGGTTTTTT TTCTTAAGTA TTTACATTAA
      GTCGTACATA GTTTTAATTA AACCAAAAAA AAGAATTCAT AAATGTAATT
--------------------------------------------------------------------------
6551  ATGGCCATAG TTGCATTAAT GAATCGGCCA ACGCGCGGGG AGAGGCGGTT
      TACCGGTATC AACGTAATTA CTTAGCCGGT TGCGCGCCCC TCTCCGCCAA
--------------------------------------------------------------------------
6601  TGCGTATTGG CGCTCTTCCG CTTCCTCGCT CACTGACTCG CTGCGCTCGG
      ACGCATAACC GCGAGAAGGC GAAGGAGCGA GTGACTGAGC GACGCGAGCC
--------------------------------------------------------------------------
6651  TCGTTCGGCT GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG
      AGCAAGCCGA CGCCGCTCGC CATAGTCGAG TGAGTTTCCG CCATTATGCC
--------------------------------------------------------------------------
```

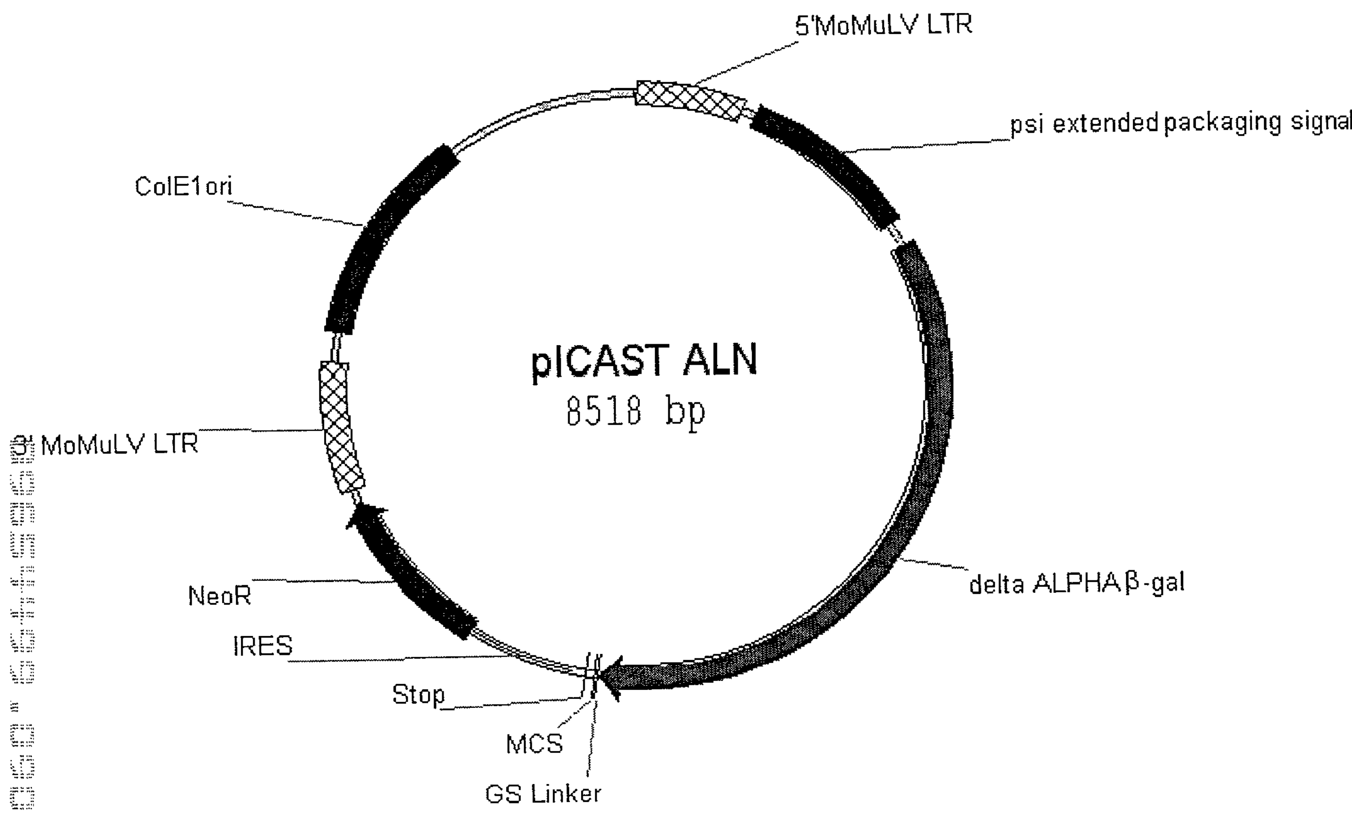
5'MoMuLV LTR
psi extended packaging signal
ColE1ori
pICAST ALN
8518 bp
3' MoMuLV LTR
NeoR
IRES
Stop
MCS
GS Linker
delta ALPHA β-gal

Figure 11A

```
1    CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG
     GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC
---------------------------------------------------------------------------
51   CCCCGGCTCA GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA
     GGGGCCGAGT CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT
---------------------------------------------------------------------------
101  GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC AAGAACAGAT
     CCTATAGACA CCATTCGTCA AGGACGGGGC CGAGTCCCGG TTCTTGTCTA
---------------------------------------------------------------------------
151  GGTCCCCAGA TGCGGTCCAG CCCTCAGCAG TTTCTAGAGA ACCATCAGAT
     CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC AAAGATCTCT TGGTAGTCTA
---------------------------------------------------------------------------
201  GTTTCCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC TTATTTGAAC
     CAAAGGTCCC ACGGGGTTCC TGGACTTTAC TGGGACACGG AATAAACTTG
---------------------------------------------------------------------------
251  TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA
     ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT
---------------------------------------------------------------------------
301  GCTCAATAAA AGAGCCCACA ACCCCTCACT CGGGGCGCCA GTCCTCCGAT
     CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA
---------------------------------------------------------------------------
351  TGACTGAGTC GCCCGGGTAC CCGTGTATCC AATAAACCCT CTTGCAGTTG
     ACTGACTCAG CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC
---------------------------------------------------------------------------
401  CATCCGACTT GTGGTCTCGC TGTTCCTTGG GAGGGTCTCC TCTGAGTGAT
     GTAGGCTGAA CACCAGAGCG ACAAGGAACC CTCCCAGAGG AGACTCACTA
---------------------------------------------------------------------------
451  TGACTACCCG TCAGCGGGGG TCTTTCATTT GGGGGCTCGT CCGGGATCGG
     ACTGATGGGC AGTCGCCCCC AGAAAGTAAA CCCCCGAGCA GGCCCTAGCC
---------------------------------------------------------------------------
501  GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG CAAGCTGGCC
     CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC GTTCGACCGG
---------------------------------------------------------------------------
551  AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA
     TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGACTAAAAT
---------------------------------------------------------------------------
601  TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC
     ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG
---------------------------------------------------------------------------
651  CGTGGTGGAA CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG
     GCACCACCTT GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC
---------------------------------------------------------------------------
701  TCCCAGGGAC TTTGGGGGCC GTTTTTGTGG CCCGACCTGA GGAAGGGAGT
     AGGGTCCCTG AAACCCCCGG CAAAAACACC GGGCTGGACT CCTTCCCTCA
---------------------------------------------------------------------------
751  CGATGTGGAA TCCGACCCCG TCAGGATATG TGGTTCTGGT AGGAGACGAG
     GCTACACCTT AGGCTGGGGC AGTCCTATAC ACCAAGACCA TCCTCTGCTC
---------------------------------------------------------------------------
801  AACCTAAAAC AGTTCCCGCC TCCGTCTGAA TTTTTGCTTT CGGTTTGGAA
     TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA GCCAAACCTT
---------------------------------------------------------------------------
851  CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT
     GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA
---------------------------------------------------------------------------
901  CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC
     GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG
---------------------------------------------------------------------------
```

FIGURE 11B

```
951   TCCCTTAAGT TTGACCTTAG GTAACTGGAA AGATGTCGAG CGGCTCGCTC
      AGGGAATTCA AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG
---------------------------------------------------------------------------
1001  ACAACCAGTC GGTAGATGTC AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT
      TGTTGGTCAG CCATCTACAG TTCTTCTCTG CAACCCAATG GAAGACGAGA
---------------------------------------------------------------------------
1051  GCAGAATGGC CAACCTTTAA CGTCGGATGG CCGCGAGACG GCACCTTTAA
      CGTCTTACCG GTTGGAAATT GCAGCCTACC GGCGCTCTGC CGTGGAAATT
---------------------------------------------------------------------------
1101  CCGAGACCTC ATCACCCAGG TTAAGATCAA GGTCTTTTCA CCTGGCCCGC
      GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT GGACCGGGCG
---------------------------------------------------------------------------
1151  ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT
      TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA
---------------------------------------------------------------------------
1201  TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC
      AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG
---------------------------------------------------------------------------
1251  TCCTCTTCCT CCATCCGCCC CGTCTCTCCC CCTTGAACCT CCTCGTTCGA
      AGGAGAAGGA GGTAGGCGGG GCAGAGAGGG GGAACTTGGA GGAGCAAGCT
---------------------------------------------------------------------------
1301  CCCCGCCTCG ATCCTCCCTT TATCCAGCCC TCACTCCTTC TCTAGGCGCC
      GGGGCGGAGC TAGGAGGGAA ATAGGTCGGG AGTGAGGAAG AGATCCGCGG
---------------------------------------------------------------------------
1351  GGCCGCTCTA GCCCATTAAT ACGACTCACT ATAGGGCGAT TCGAACACCA
      CCGGCGAGAT CGGGTAATTA TGCTGAGTGA TATCCCGCTA AGCTTGTGGT
---------------------------------------------------------------------------
1401  TGCACCATCA TCATCATCAC GTCGACTATA AAGATGAGGA CCTCGAGATG
      ACGTGGTAGT AGTAGTAGTG CAGCTGATAT TTCTACTCCT GGAGCTCTAC
---------------------------------------------------------------------------
1451  GGCGTGATTA CGGATTCACT GGCCGTCGTG GCCCGCACCG ATCGCCCTTC
      CCGCACTAAT GCCTAAGTGA CCGGCAGCAC CGGGCGTGGC TAGCGGGAAG
---------------------------------------------------------------------------
1501  CCAACAGTTA CGCAGCCTGA ATGGCGAATG GCGCTTTGCC TGGTTTCCGG
      GGTTGTCAAT GCGTCGGACT TACCGCTTAC CGCGAAACGG ACCAAAGGCC
---------------------------------------------------------------------------
1551  CACCAGAAGC GGTGCCGGAA AGCTGGCTGG AGTGCGATCT TCCTGAGGCC
      GTGGTCTTCG CCACGGCCTT TCGACCGACC TCACGCTAGA AGGACTCCGG
---------------------------------------------------------------------------
1601  GATACTGTCG TCGTCCCCTC AAACTGGCAG ATGCACGGTT ACGATGCGCC
      CTATGACAGC AGCAGGGGAG TTTGACCGTC TACGTGCCAA TGCTACGCGG
---------------------------------------------------------------------------
1651  CATCTACACC AACGTGACCT ATCCCATTAC GGTCAATCCG CCGTTTGTTC
      GTAGATGTGG TTGCACTGGA TAGGGTAATG CCAGTTAGGC GGCAAACAAG
---------------------------------------------------------------------------
1701  CCACGGAGAA TCCGACGGGT TGTTACTCGC TCACATTTAA TGTTGATGAA
      GGTGCCTCTT AGGCTGCCCA ACAATGAGCG AGTGTAAATT ACAACTACTT
---------------------------------------------------------------------------
1751  AGCTGGCTAC AGGAAGGCCA GACGCGAATT ATTTTTGATG GCGTTAACTC
      TCGACCGATG TCCTTCCGGT CTGCGCTTAA TAAAAACTAC CGCAATTGAG
---------------------------------------------------------------------------
1801  GGCGTTTCAT CTGTGGTGCA ACGGGCGCTG GGTCGGTTAC GGCCAGGACA
      CCGCAAAGTA GACACCACGT TGCCCGCGAC CCAGCCAATG CCGGTCCTGT
---------------------------------------------------------------------------
1851  GTCGTTTGCC GTCTGAATTT GACCTGAGCG CATTTTTACG CGCCGGAGAA
      CAGCAAACGG CAGACTTAAA CTGGACTCGC GTAAAAATGC GCGGCCTCTT
---------------------------------------------------------------------------
```

```
1901  AACCGCCTCG CGGTGATGGT GCTGCGCTGG AGTGACGGCA GTTATCTGGA
      TTGGCGGAGC GCCACTACCA CGACGCGACC TCACTGCCGT CAATAGACCT
-------------------------------------------------------------
1951  AGATCAGGAT ATGTGGCGGA TGAGCGGCAT TTTCCGTGAC GTCTCGTTGC
      TCTAGTCCTA TACACCGCCT ACTCGCCGTA AAAGGCACTG CAGAGCAACG
-------------------------------------------------------------
2001  TGCATAAACC GACTACACAA ATCAGCGATT TCCATGTTGC CACTCGCTTT
      ACGTATTTGG CTGATGTGTT TAGTCGCTAA AGGTACAACG GTGAGCGAAA
-------------------------------------------------------------
2051  AATGATGATT TCAGCCGCGC TGTACTGGAG GCTGAAGTTC AGATGTGCGG
      TTACTACTAA AGTCGGCGCG ACATGACCTC CGACTTCAAG TCTACACGCC
-------------------------------------------------------------
2101  CGAGTTGCGT GACTACCTAC GGGTAACAGT TTCTTTATGG CAGGGTGAAA
      GCTCAACGCA CTGATGGATG CCCATTGTCA AAGAAATACC GTCCCACTTT
-------------------------------------------------------------
2151  CGCAGGTCGC CAGCGGCACC GCGCCTTTCG GCGGTGAAAT TATCGATGAG
      GCGTCCAGCG GTCGCCGTGG CGCGGAAAGC CGCCACTTTA ATAGCTACTC
-------------------------------------------------------------
2201  CGTGGTGGTT ATGCCGATCG CGTCACACTA CGTCTGAACG TCGAAAACCC
      GCACCACCAA TACGGCTAGC GCAGTGTGAT GCAGACTTGC AGCTTTTGGG
-------------------------------------------------------------
2251  GAAACTGTGG AGCGCCGAAA TCCCGAATCT CTATCGTGCG GTGGTTGAAC
      CTTTGACACC TCGCGGCTTT AGGGCTTAGA GATAGCACGC CACCAACTTG
-------------------------------------------------------------
2301  TGCACACCGC CGACGGCACG CTGATTGAAG CAGAAGCCTG CGATGTCGGT
      ACGTGTGGCG GCTGCCGTGC GACTAACTTC GTCTTCGGAC GCTACAGCCA
-------------------------------------------------------------
2351  TTCCGCGAGG TGCGGATTGA AAATGGTCTG CTGCTGCTGA ACGGCAAGCC
      AAGGCGCTCC ACGCCTAACT TTTACCAGAC GACGACGACT TGCCGTTCGG
-------------------------------------------------------------
2401  GTTGCTGATT CGAGGCGTTA ACCGTCACGA GCATCATCCT CTGCATGGTC
      CAACGACTAA GCTCCGCAAT TGGCAGTGCT CGTAGTAGGA GACGTACCAG
-------------------------------------------------------------
2451  AGGTCATGGA TGAGCAGACG ATGGTGCAGG ATATCCTGCT GATGAAGCAG
      TCCAGTACCT ACTCGTCTGC TACCACGTCC TATAGGACGA CTACTTCGTC
-------------------------------------------------------------
2501  AACAACTTTA ACGCCGTGCG CTGTTCGCAT TATCCGAACC ATCCGCTGTG
      TTGTTGAAAT TGCGGCACGC GACAAGCGTA ATAGGCTTGG TAGGCGACAC
-------------------------------------------------------------
2551  GTACACGCTG TGCGACCGCT ACGGCCTGTA TGTGGTGGAT GAAGCCAATA
      CATGTGCGAC ACGCTGGCGA TGCCGGACAT ACACCACCTA CTTCGGTTAT
-------------------------------------------------------------
2601  TTGAAACCCA CGGCATGGTG CCAATGAATC GTCTGACCGA TGATCCGCGC
      AACTTTGGGT GCCGTACCAC GGTTACTTAG CAGACTGGCT ACTAGGCGCG
-------------------------------------------------------------
2651  TGGCTACCGG CGATGAGCGA ACGCGTAACG CGAATGGTGC AGCGCGATCG
      ACCGATGGCC GCTACTCGCT TGCGCATTGC GCTTACCACG TCGCGCTAGC
-------------------------------------------------------------
2701  TAATCACCCG AGTGTGATCA TCTGGTCGCT GGGGAATGAA TCAGGCCACG
      ATTAGTGGGC TCACACTAGT AGACCAGCGA CCCCTTACTT AGTCCGGTGC
-------------------------------------------------------------
2751  GCGCTAATCA CGACGCGCTG TATCGCTGGA TCAAATCTGT CGATCCTTCC
      CGCGATTAGT GCTGCGCGAC ATAGCGACCT AGTTTAGACA GCTAGGAAGG
-------------------------------------------------------------
2801  CGCCCGGTGC AGTATGAAGG CGGCGGAGCC GACACCACGG CCACCGATAT
      GCGGGCCACG TCATACTTCC GCCGCCTCGG CTGTGGTGCC GGTGGCTATA
-------------------------------------------------------------
```

```
2851  TATTTGCCCG ATGTACGCGC GCGTGGATGA AGACCAGCCC TTCCCGGCTG
      ATAAACGGGC TACATGCGCG CGCACCTACT TCTGGTCGGG AAGGGCCGAC
-----------------------------------------------------------------
2901  TGCCGAAATG GTCCATCAAA AAATGGCTTT CGCTACCTGG AGAGACGCGC
      ACGGCTTTAC CAGGTAGTTT TTTACCGAAA GCGATGGACC TCTCTGCGCG
-----------------------------------------------------------------
2951  CCGCTGATCC TTTGCGAATA CGCCCACGCG ATGGGTAACA GTCTTGGCGG
      GGCGACTAGG AAACGCTTAT GCGGGTGCGC TACCCATTGT CAGAACCGCC
-----------------------------------------------------------------
3001  TTTCGCTAAA TACTGGCAGG CGTTTCGTCA GTATCCCCGT TTACAGGGCG
      AAAGCGATTT ATGACCGTCC GCAAAGCAGT CATAGGGGCA AATGTCCCGC
-----------------------------------------------------------------
3051  GCTTCGTCTG GGACTGGGTG GATCAGTCGC TGATTAAATA TGATGAAAAC
      CGAAGCAGAC CCTGACCCAC CTAGTCAGCG ACTAATTTAT ACTACTTTTG
-----------------------------------------------------------------
3101  GGCAACCCGT GGTCGGCTTA CGGCGGTGAT TTTGGCGATA CGCCGAACGA
      CCGTTGGGCA CCAGCCGAAT GCCGCCACTA AAACCGCTAT GCGGCTTGCT
-----------------------------------------------------------------
3151  TCGCCAGTTC TGTATGAACG GTCTGGTCTT TGCCGACCGC ACGCCGCATC
      AGCGGTCAAG ACATACTTGC CAGACCAGAA ACGGCTGGCG TGCGGCGTAG
-----------------------------------------------------------------
3201  CAGCGCTGAC GGAAGCAAAA CACCAGCAGC AGTTTTTCCA GTTCCGTTTA
      GTCGCGACTG CCTTCGTTTT GTGGTCGTCG TCAAAAAGGT CAAGGCAAAT
-----------------------------------------------------------------
3251  TCCGGGCAAA CCATCGAAGT GACCAGCGAA TACCTGTTCC GTCATAGCGA
      AGGCCCGTTT GGTAGCTTCA CTGGTCGCTT ATGGACAAGG CAGTATCGCT
-----------------------------------------------------------------
3301  TAACGAGCTC CTGCACTGGA TGGTGGCGCT GGATGGTAAG CCGCTGGCAA
      ATTGCTCGAG GACGTGACCT ACCACCGCGA CCTACCATTC GGCGACCGTT
-----------------------------------------------------------------
3351  GCGGTGAAGT GCCTCTGGAT GTCGCTCCAC AAGGTAAACA GTTGATTGAA
      CGCCACTTCA CGGAGACCTA CAGCGAGGTG TTCCATTTGT CAACTAACTT
-----------------------------------------------------------------
3401  CTGCCTGAAC TACCGCAGCC GGAGAGCGCC GGGCAACTCT GGCTCACAGT
      GACGGACTTG ATGGCGTCGG CCTCTCGCGG CCCGTTGAGA CCGAGTGTCA
-----------------------------------------------------------------
3451  ACGCGTAGTG CAACCGAACG CGACCGCATG GTCAGAAGCC GGGCACATCA
      TGCGCATCAC GTTGGCTTGC GCTGGCGTAC CAGTCTTCGG CCCGTGTAGT
-----------------------------------------------------------------
3501  GCGCCTGGCA GCAGTGGCGT CTGGCGGAAA ACCTCAGTGT GACGCTCCCC
      CGCGGACCGT CGTCACCGCA GACCGCCTTT TGGAGTCACA CTGCGAGGGG
-----------------------------------------------------------------
3551  GCCGCGTCCC ACGCCATCCC GCATCTGACC ACCAGCGAAA TGGATTTTTG
      CGGCGCAGGG TGCGGTAGGG CGTAGACTGG TGGTCGCTTT ACCTAAAAAC
-----------------------------------------------------------------
3601  CATCGAGCTG GGTAATAAGC GTTGGCAATT TAACCGCCAG TCAGGCTTTC
      GTAGCTCGAC CCATTATTCG CAACCGTTAA ATTGGCGGTC AGTCCGAAAG
-----------------------------------------------------------------
3651  TTTCACAGAT GTGGATTGGC GATAAAAAAC AACTGCTGAC GCCGCTGCGC
      AAAGTGTCTA CACCTAACCG CTATTTTTTG TTGACGACTG CGGCGACGCG
-----------------------------------------------------------------
3701  GATCAGTTCA CCCGTGCACC GCTGGATAAC GACATTGGCG TAAGTGAAGC
      CTAGTCAAGT GGGCACGTGG CGACCTATTG CTGTAACCGC ATTCACTTCG
-----------------------------------------------------------------
3751  GACCCGCATT GACCCTAACG CCTGGGTCGA ACGCTGGAAG GCGGCGGGCC
      CTGGGCGTAA CTGGGATTGC GGACCCAGCT TGCGACCTTC CGCCGCCCGG
-----------------------------------------------------------------
```

```
3801  ATTACCAGGC CGAAGCAGCG TTGTTGCAGT GCACGGCAGA TACACTTGCT
      TAATGGTCCG GCTTCGTCGC AACAACGTCA CGTGCCGTCT ATGTGAACGA
----------------------------------------------------------------------------
3851  GATGCGGTGC TGATTACGAC CGCTCACGCG TGGCAGCATC AGGGGAAAAC
      CTACGCCACG ACTAATGCTG GCGAGTGCGC ACCGTCGTAG TCCCCTTTTG
----------------------------------------------------------------------------
3901  CTTATTTATC AGCCGGAAAA CCTACCGGAT TGATGGTAGT GGTCAAATGG
      GAATAAATAG TCGGCCTTTT GGATGGCCTA ACTACCATCA CCAGTTTACC
----------------------------------------------------------------------------
3951  CGATTACCGT TGATGTTGAA GTGGCGAGCG ATACACCGCA TCCGGCGCGG
      GCTAATGGCA ACTACAACTT CACCGCTCGC TATGTGGCGT AGGCCGCGCC
----------------------------------------------------------------------------
4001  ATTGGCCTGA ACTGCCAGCT GGCGCAGGTA GCAGAGCGGG TAAACTGGCT
      TAACCGGACT TGACGGTCGA CCGCGTCCAT CGTCTCGCCC ATTTGACCGA
----------------------------------------------------------------------------
4051  CGGATTAGGG CCGCAAGAAA ACTATCCCGA CCGCCTTACT GCCGCCTGTT
      GCCTAATCCC GGCGTTCTTT TGATAGGGCT GGCGGAATGA CGGCGGACAA
----------------------------------------------------------------------------
4101  TTGACCGCTG GGATCTGCCA TTGTCAGACA TGTATACCCC GTACGTCTTC
      AACTGGCGAC CCTAGACGGT AACAGTCTGT ACATATGGGG CATGCAGAAG
----------------------------------------------------------------------------
4151  CCGAGCGAAA ACGGTCTGCG CTGCGGGACG CGCGAATTGA ATTATGGCCC
      GGCTCGCTTT TGCCAGACGC GACGCCCTGC GCGCTTAACT TAATACCGGG
----------------------------------------------------------------------------
4201  ACACCAGTGG CGCGGCGACT TCCAGTTCAA CATCAGCCGC TACAGTCAAC
      TGTGGTCACC GCGCCGCTGA AGGTCAAGTT GTAGTCGGCG ATGTCAGTTG
----------------------------------------------------------------------------
4251  AGCAACTGAT GGAAACCAGC CATCGCCATC TGCTGCACGC GGAAGAAGGC
      TCGTTGACTA CCTTTGGTCG GTAGCGGTAG ACGACGTGCG CCTTCTTCCG
----------------------------------------------------------------------------
4301  ACATGGCTGA ATATCGACGG TTTCCATATG GGGATTGGTG GCGACGACTC
      TGTACCGACT TATAGCTGCC AAAGGTATAC CCCTAACCAC CGCTGCTGAG
----------------------------------------------------------------------------
4351  CTGGAGCCCG TCAGTATCGG CGGAATTCCA GCTGAGCGCC GGTCGCTACC
      GACCTCGGGC AGTCATAGCC GCCTTAAGGT CGACTCGCGG CCAGCGATGG
----------------------------------------------------------------------------
4401  ATTACCAGTT GGTCTGGTGT CAAAAAAGAT CTGGAGGTGG TGGCAGCAGG
      TAATGGTCAA CCAGACCACA GTTTTTTCTA GACCTCCACC ACCGTCGTCC
----------------------------------------------------------------------------
4451  CCTTGGCGCG CCGGATCCTT AATTAACAAT TGACCGGTAA TAATAGGTAG
      GGAACCGCGC GGCCTAGGAA TTAATTGTTA ACTGGCCATT ATTATCCATC
----------------------------------------------------------------------------
4501  ATAAGTGACT GATTAGATGC ATTGATCCCT CGACCAATTC CGGTTATTTT
      TATTCACTGA CTAATCTACG TAACTAGGGA GCTGGTTAAG GCCAATAAAA
----------------------------------------------------------------------------
4551  CCACCATATT GCCGTCTTTT GGCAATGTGA GGGCCCGGAA ACCTGGCCCT
      GGTGGTATAA CGGCAGAAAA CCGTTACACT CCCGGGCCTT TGGACCGGGA
----------------------------------------------------------------------------
4601  GTCTTCTTGA CGAGCATTCC TAGGGGTCTT TCCCCTCTCG CCAAAGGAAT
      CAGAAGAACT GCTCGTAAGG ATCCCCAGAA AGGGGAGAGC GGTTTCCTTA
----------------------------------------------------------------------------
4651  GCAAGGTCTG TTGAATGTCG TGAAGGAAGC AGTTCCTCTG GAAGCTTCTT
      CGTTCCAGAC AACTTACAGC ACTTCCTTCG TCAAGGAGAC CTTCGAAGAA
----------------------------------------------------------------------------
4701  GAAGACAAAC AACGTCTGTA GCGACCCTTT GCAGGCAGCG GAACCCCCCA
      CTTCTGTTTG TTGCAGACAT CGCTGGGAAA CGTCCGTCGC CTTGGGGGGT
----------------------------------------------------------------------------
```

```
4751  CCTGGCGACA GGTGCCTCTG CGGCCAAAAG CCACGTGTAT AAGATACACC
      GGACCGCTGT CCACGGAGAC GCCGGTTTTC GGTGCACATA TTCTATGTGG
------------------------------------------------------------------------
4801  TGCAAAGGCG GCACAACCCC AGTGCCACGT TGTGAGTTGG ATAGTTGTGG
      ACGTTTCCGC CGTGTTGGGG TCACGGTGCA ACACTCAACC TATCAACACC
------------------------------------------------------------------------
4851  AAAGAGTCAA ATGGCTCTCC TCAAGCGTAT TCAACAAGGG GCTGAAGGAT
      TTTCTCAGTT TACCGAGAGG AGTTCGCATA AGTTGTTCCC CGACTTCCTA
------------------------------------------------------------------------
4901  GCCCAGAAGG TACCCCATTG TATGGGATCT GATCTGGGGC CTCGGTGCAC
      CGGGTCTTCC ATGGGGTAAC ATACCCTAGA CTAGACCCCG GAGCCACGTG
------------------------------------------------------------------------
4951  ATGCTTTACA TGTGTTTAGT CGAGGTTAAA AAACGTCTAG GCCCCCCGAA
      TACGAAATGT ACACAAATCA GCTCCAATTT TTTGCAGATC CGGGGGGCTT
------------------------------------------------------------------------
5001  CCACGGGGAC GTGGTTTTCC TTTGAAAAAC ACGATGATAA TACCATGATT
      GGTGCCCCTG CACCAAAAGG AAACTTTTTG TGCTACTATT ATGGTACTAA
------------------------------------------------------------------------
5051  GAACAAGATG GATTGCACGC AGGTTCTCCG GCCGCTTGGG TGGAGAGGCT
      CTTGTTCTAC CTAACGTGCG TCCAAGAGGC CGGCGAACCC ACCTCTCCGA
------------------------------------------------------------------------
5101  ATTCGGCTAT GACTGGGCAC AACAGACAAT CGGCTGCTCT GATGCCGCCG
      TAAGCCGATA CTGACCCGTG TTGTCTGTTA GCCGACGAGA CTACGGCGGC
------------------------------------------------------------------------
5151  TGTTCCGGCT GTCAGCGCAG GGGCGCCCGG TTCTTTTTGT CAAGACCGAC
      ACAAGGCCGA CAGTCGCGTC CCCGCGGGCC AAGAAAAACA GTTCTGGCTG
------------------------------------------------------------------------
5201  CTGTCCGGTG CCCTGAATGA ACTGCAGGAC GAGGCAGCGC GGCTATCGTG
      GACAGGCCAC GGGACTTACT TGACGTCCTG CTCCGTCGCG CCGATAGCAC
------------------------------------------------------------------------
5251  GCTGGCCACG ACGGGCGTTC CTTGCGCAGC TGTGCTCGAC GTTGTCACTG
      CGACCGGTGC TGCCCGCAAG GAACGCGTCG ACACGAGCTG CAACAGTGAC
------------------------------------------------------------------------
5301  AAGCGGGAAG GGACTGGCTG CTATTGGGCG AAGTGCCGGG GCAGGATCTC
      TTCGCCCTTC CCTGACCGAC GATAACCCGC TTCACGGCCC CGTCCTAGAG
------------------------------------------------------------------------
5351  CTGTCATCTC ACCTTGCTCC TGCCGAGAAA GTATCCATCA TGGCTGATGC
      GACAGTAGAG TGGAACGAGG ACGGCTCTTT CATAGGTAGT ACCGACTACG
------------------------------------------------------------------------
5401  AATGCGGCGG CTGCATACGC TTGATCCGGC TACCTGCCCA TTCGACCACC
      TTACGCCGCC GACGTATGCG AACTAGGCCG ATGGACGGGT AAGCTGGTGG
------------------------------------------------------------------------
5451  AAGCGAAACA TCGCATCGAG CGAGCACGTA CTCGGATGGA AGCCGGTCTT
      TTCGCTTTGT AGCGTAGCTC GCTCGTGCAT GAGCCTACCT TCGGCCAGAA
------------------------------------------------------------------------
5501  GTCGATCAGG ATGATCTGGA CGAAGAGCAT CAGGGGCTCG CGCCAGCCGA
      CAGCTAGTCC TACTAGACCT GCTTCTCGTA GTCCCCGAGC GCGGTCGGCT
------------------------------------------------------------------------
5551  ACTGTTCGCC AGGCTCAAGG CGCGCATGCC CGACGGCGAG GATCTCGTCG
      TGACAAGCGG TCCGAGTTCC GCGCGTACGG GCTGCCGCTC CTAGAGCAGC
------------------------------------------------------------------------
5601  TGACCCATGG CGATGCCTGC TTGCCGAATA TCATGGTGGA AAATGGCCGC
      ACTGGGTACC GCTACGGACG AACGGCTTAT AGTACCACCT TTTACCGGCG
------------------------------------------------------------------------
5651  TTTTCTGGAT TCATCGACTG TGGCCGGCTG GGTGTGGCGG ACCGCTATCA
      AAAAGACCTA AGTAGCTGAC ACCGGCCGAC CCACACCGCC TGGCGATAGT
------------------------------------------------------------------------
```

```
5701  GGACATAGCG TTGGCTACCC GTGATATTGC TGAAGAGCTT GGCGGCGAAT
      CCTGTATCGC AACCGATGGG CACTATAACG ACTTCTCGAA CCGCCGCTTA
---------------------------------------------------------------------------
5751  GGGCTGACCG CTTCCTCGTG CTTTACGGTA TCGCCGCTCC CGATTCGCAG
      CCCGACTGGC GAAGGAGCAC GAAATGCCAT AGCGGCGAGG GCTAAGCGTC
---------------------------------------------------------------------------
5801  CGCATCGCCT TCTATCGCCT TCTTGACGAG TTCTTCTGAG CGGGACTCTG
      GCGTAGCGGA AGATAGCGGA AGAACTGCTC AAGAAGACTC GCCCTGAGAC
---------------------------------------------------------------------------
5851  GGGTTCGCAT CGATAAAATA AAAGATTTTA TTTAGTCTCC AGAAAAAGGG
      CCCAAGCGTA GCTATTTTAT TTTCTAAAAT AAATCAGAGG TCTTTTTCCC
---------------------------------------------------------------------------
5901  GGGAATGAAA GACCCCACCT GTAGGTTTGG CAAGCTAGCT TAAGTAACGC
      CCCTTACTTT CTGGGGTGGA CATCCAAACC GTTCGATCGA ATTCATTGCG
---------------------------------------------------------------------------
5951  CATTTTGCAA GGCATGGAAA AATACATAAC TGAGAATAGA GAAGTTCAGA
      GTAAAACGTT CCGTACCTTT TTATGTATTG ACTCTTATCT CTTCAAGTCT
---------------------------------------------------------------------------
6001  TCAAGGTCAG GAACAGATGG AACAGCTGAA TATGGGCCAA ACAGGATATC
      AGTTCCAGTC CTTGTCTACC TTGTCGACTT ATACCCGGTT TGTCCTATAG
---------------------------------------------------------------------------
6051  TGTGGTAAGC AGTTCCTGCC CCGGCTCAGG GCCAAGAACA GATGGAACAG
      ACACCATTCG TCAAGGACGG GGCCGAGTCC CGGTTCTTGT CTACCTTGTC
---------------------------------------------------------------------------
6101  CTGAATATGG GCCAAACAGG ATATCTGTGG TAAGCAGTTC CTGCCCCGGC
      GACTTATACC CGGTTTGTCC TATAGACACC ATTCGTCAAG GACGGGGCCG
---------------------------------------------------------------------------
6151  TCAGGGCCAA GAACAGATGG TCCCCAGATG CGGTCCAGCC CTCAGCAGTT
      AGTCCCGGTT CTTGTCTACC AGGGGTCTAC GCCAGGTCGG GAGTCGTCAA
---------------------------------------------------------------------------
6201  TCTAGAGAAC CATCAGATGT TTCCAGGGTG CCCCAAGGAC CTGAAATGAC
      AGATCTCTTG GTAGTCTACA AAGGTCCCAC GGGGTTCCTG GACTTTACTG
---------------------------------------------------------------------------
6251  CCTGTGCCTT ATTTGAACTA ACCAATCAGT TCGCTTCTCG CTTCTGTTCG
      GGACACGGAA TAAACTTGAT TGGTTAGTCA AGCGAAGAGC GAAGACAAGC
---------------------------------------------------------------------------
6301  CGCGCTTCTG CTCCCCGAGC TCAATAAAAG AGCCCACAAC CCCTCACTCG
      GCGCGAAGAC GAGGGGCTCG AGTTATTTTC TCGGGTGTTG GGGAGTGAGC
---------------------------------------------------------------------------
6351  GGGCGCCAGT CCTCCGATTG ACTGAGTCGC CCGGGTACCC GTGTATCCAA
      CCCGCGGTCA GGAGGCTAAC TGACTCAGCG GGCCCATGGG CACATAGGTT
---------------------------------------------------------------------------
6401  TAAACCCTCT TGCAGTTGCA TCCGACTTGT GGTCTCGCTG TTCCTTGGGA
      ATTTGGGAGA ACGTCAACGT AGGCTGAACA CCAGAGCGAC AAGGAACCCT
---------------------------------------------------------------------------
6451  GGGTCTCCTC TGAGTGATTG ACTACCCGTC AGCGGGGGTC TTTCATTCAT
      CCCAGAGGAG ACTCACTAAC TGATGGGCAG TCGCCCCCAG AAAGTAAGTA
---------------------------------------------------------------------------
6501  GCAGCATGTA TCAAAATTAA TTTGGTTTTT TTTCTTAAGT ATTTACATTA
      CGTCGTACAT AGTTTTAATT AAACCAAAAA AAAGAATTCA TAAATGTAAT
---------------------------------------------------------------------------
6551  AATGGCCATA GTTGCATTAA TGAATCGGCC AACGCGCGGG GAGAGGCGGT
      TTACCGGTAT CAACGTAATT ACTTAGCCGG TTGCGCGCCC CTCTCCGCCA
---------------------------------------------------------------------------
6601  TTGCGTATTG GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG
      AACGCATAAC CGCGAGAAGG CGAAGGAGCG AGTGACTGAG CGACGCGAGC
---------------------------------------------------------------------------
```

```
6651  GTCGTTCGGC TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG
      CAGCAAGCCG ACGCCGCTCG CCATAGTCGA GTGAGTTTCC GCCATTATGC
-------------------------------------------------------------------------------
6701  GTTATCCACA GAATCAGGGG ATAACGCAGG AAAGAACATG TGAGCAAAAG
      CAATAGGTGT CTTAGTCCCC TATTGCGTCC TTTCTTGTAC ACTCGTTTTC
-------------------------------------------------------------------------------
6751  GCCAGCAAAA GGCCAGGAAC CGTAAAAAGG CCGCGTTGCT GGCGTTTTTC
      CGGTCGTTTT CCGGTCCTTG GCATTTTTCC GGCGCAACGA CCGCAAAAAG
-------------------------------------------------------------------------------
6801  CATAGGCTCC GCCCCCCTGA CGAGCATCAC AAAAATCGAC GCTCAAGTCA
      GTATCCGAGG CGGGGGGACT GCTCGTAGTG TTTTTAGCTG CGAGTTCAGT
-------------------------------------------------------------------------------
6851  GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG TTTCCCCCTG
      CTCCACCGCT TTGGGCTGTC CTGATATTTC TATGGTCCGC AAAGGGGGAC
-------------------------------------------------------------------------------
6901  GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC
      CTTCGAGGGA GCACGCGAGA GGACAAGGCT GGGACGGCGA ATGGCCTATG
-------------------------------------------------------------------------------
6951  CTGTCCGCCT TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC ATAGCTCACG
      GACAGGCGGA AAGAGGGAAG CCCTTCGCAC CGCGAAAGAG TATCGAGTGC
-------------------------------------------------------------------------------
7001  CTGTAGGTAT CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG
      GACATCCATA GAGTCAAGCC ACATCCAGCA AGCGAGGTTC GACCCGACAC
-------------------------------------------------------------------------------
7051  TGCACGAACC CCCCGTTCAG CCCGACCGCT GCGCCTTATC CGGTAACTAT
      ACGTGCTTGG GGGGCAAGTC GGGCTGGCGA CGCGGAATAG GCCATTGATA
-------------------------------------------------------------------------------
7101  CGTCTTGAGT CCAACCCGGT AAGACACGAC TTATCGCCAC TGGCAGCAGC
      GCAGAACTCA GGTTGGGCCA TTCTGTGCTG AATAGCGGTG ACCGTCGTCG
-------------------------------------------------------------------------------
7151  CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT GCTACAGAGT
      GTGACCATTG TCCTAATCGT CTCGCTCCAT ACATCCGCCA CGATGTCTCA
-------------------------------------------------------------------------------
7201  TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGAAC AGTATTTGGT
      AGAACTTCAC CACCGGATTG ATGCCGATGT GATCTTCTTG TCATAAACCA
-------------------------------------------------------------------------------
7251  ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC
      TAGACGCGAG ACGACTTCGG TCAATGGAAG CCTTTTTCTC AACCATCGAG
-------------------------------------------------------------------------------
7301  TTGATCCGGC AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA
      AACTAGGCCG TTTGTTTGGT GGCGACCATC GCCACCAAAA AAACAAACGT
-------------------------------------------------------------------------------
7351  AGCAGCAGAT TACGCGCAGA AAAAAAGGAT CTCAAGAAGA TCCTTTGATC
      TCGTCGTCTA ATGCGCGTCT TTTTTTCCTA GAGTTCTTCT AGGAAACTAG
-------------------------------------------------------------------------------
7401  TTTTCTACGG GGTCTGACGC TCAGTGGAAC GAAAACTCAC GTTAAGGGAT
      AAAAGATGCC CCAGACTGCG AGTCACCTTG CTTTTGAGTG CAATTCCCTA
-------------------------------------------------------------------------------
7451  TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC CTTTTGCGGC
      AAACCAGTAC TCTAATAGTT TTTCCTAGAA GTGGATCTAG GAAAACGCCG
-------------------------------------------------------------------------------
7501  CGCAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG ACAGTTACCA
      GCGTTTAGTT AGATTTCATA TATACTCATT TGAACCAGAC TGTCAATGGT
-------------------------------------------------------------------------------
7551  ATGCTTAATC AGTGAGGCAC CTATCTCAGC GATCTGTCTA TTTCGTTCAT
      TACGAATTAG TCACTCCGTG GATAGAGTCG CTAGACAGAT AAAGCAAGTA
-------------------------------------------------------------------------------
```

```
7601  CCATAGTTGC CTGACTCCCC GTCGTGTAGA TAACTACGAT ACGGGAGGGC
      GGTATCAACG GACTGAGGGG CAGCACATCT ATTGATGCTA TGCCCTCCCG
----------------------------------------------------------------------
7651  TTACCATCTG GCCCCAGTGC TGCAATGATA CCGCGAGACC CACGCTCACC
      AATGGTAGAC CGGGGTCACG ACGTTACTAT GGCGCTCTGG GTGCGAGTGG
----------------------------------------------------------------------
7701  GGCTCCAGAT TTATCAGCAA TAAACCAGCC AGCCGGAAGG GCCGAGCGCA
      CCGAGGTCTA AATAGTCGTT ATTTGGTCGG TCGGCCTTCC CGGCTCGCGT
----------------------------------------------------------------------
7751  GAAGTGGTCC TGCAACTTTA TCCGCCTCCA TCCAGTCTAT TAATTGTTGC
      CTTCACCAGG ACGTTGAAAT AGGCGGAGGT AGGTCAGATA ATTAACAACG
----------------------------------------------------------------------
7801  CGGGAAGCTA GAGTAAGTAG TTCGCCAGTT AATAGTTTGC GCAACGTTGT
      GCCCTTCGAT CTCATTCATC AAGCGGTCAA TTATCAAACG CGTTGCAACA
----------------------------------------------------------------------
7851  TGCCATTGCT ACAGGCATCG TGGTGTCACG CTCGTCGTTT GGTATGGCTT
      ACGGTAACGA TGTCCGTAGC ACCACAGTGC GAGCAGCAAA CCATACCGAA
----------------------------------------------------------------------
7901  CATTCAGCTC CGGTTCCCAA CGATCAAGGC GAGTTACATG ATCCCCCATG
      GTAAGTCGAG GCCAAGGGTT GCTAGTTCCG CTCAATGTAC TAGGGGGTAC
----------------------------------------------------------------------
7951  TTGTGCAAAA AAGCGGTTAG CTCCTTCGGT CCTCCGATCG TTGTCAGAAG
      AACACGTTTT TTCGCCAATC GAGGAAGCCA GGAGGCTAGC AACAGTCTTC
----------------------------------------------------------------------
8001  TAAGTTGGCC GCAGTGTTAT CACTCATGGT TATGGCAGCA CTGCATAATT
      ATTCAACCGG CGTCACAATA GTGAGTACCA ATACCGTCGT GACGTATTAA
----------------------------------------------------------------------
8051  CTCTTACTGT CATGCCATCC GTAAGATGCT TTTCTGTGAC TGGTGAGTAC
      GAGAATGACA GTACGGTAGG CATTCTACGA AAAGACACTG ACCACTCATG
----------------------------------------------------------------------
8101  TCAACCAAGT CATTCTGAGA ATAGTGTATG CGGCGACCGA GTTGCTCTTG
      AGTTGGTTCA GTAAGACTCT TATCACATAC GCCGCTGGCT CAACGAGAAC
----------------------------------------------------------------------
8151  CCCGGCGTCA ATACGGGATA ATACCGCGCC ACATAGCAGA ACTTTAAAAG
      GGGCCGCAGT TATGCCCTAT TATGGCGCGG TGTATCGTCT TGAAATTTTC
----------------------------------------------------------------------
8201  TGCTCATCAT TGGAAAACGT TCTTCGGGGC GAAAACTCTC AAGGATCTTA
      ACGAGTAGTA ACCTTTTGCA AGAAGCCCCG CTTTTGAGAG TTCCTAGAAT
----------------------------------------------------------------------
8251  CCGCTGTTGA GATCCAGTTC GATGTAACCC ACTCGTGCAC CCAACTGATC
      GGCGACAACT CTAGGTCAAG CTACATTGGG TGAGCACGTG GGTTGACTAG
----------------------------------------------------------------------
8301  TTCAGCATCT TTTACTTTCA CCAGCGTTTC TGGGTGAGCA AAAACAGGAA
      AAGTCGTAGA AAATGAAAGT GGTCGCAAAG ACCCACTCGT TTTTGTCCTT
----------------------------------------------------------------------
8351  GGCAAAATGC CGCAAAAAAG GGAATAAGGG CGACACGGAA ATGTTGAATA
      CCGTTTTACG GCGTTTTTTC CCTTATTCCC GCTGTGCCTT TACAACTTAT
----------------------------------------------------------------------
8401  CTCATACTCT TCCTTTTTCA ATATTATTGA AGCATTTATC AGGGTTATTG
      GAGTATGAGA AGGAAAAAGT TATAATAACT TCGTAAATAG TCCCAATAAC
----------------------------------------------------------------------
8451  TCTCATGAGC GGATACATAT TTGAATGTAT TTAGAAAAAT AAACAAATAG
      AGAGTACTCG CCTATGTATA AACTTACATA AATCTTTTTA TTTGTTTATC
----------------------------------------------------------------------
8501  GGGTTCCGCG CACATTTC
      CCCAAGGCGC GTGTAAAG
----------------------------------------------------------------------
```

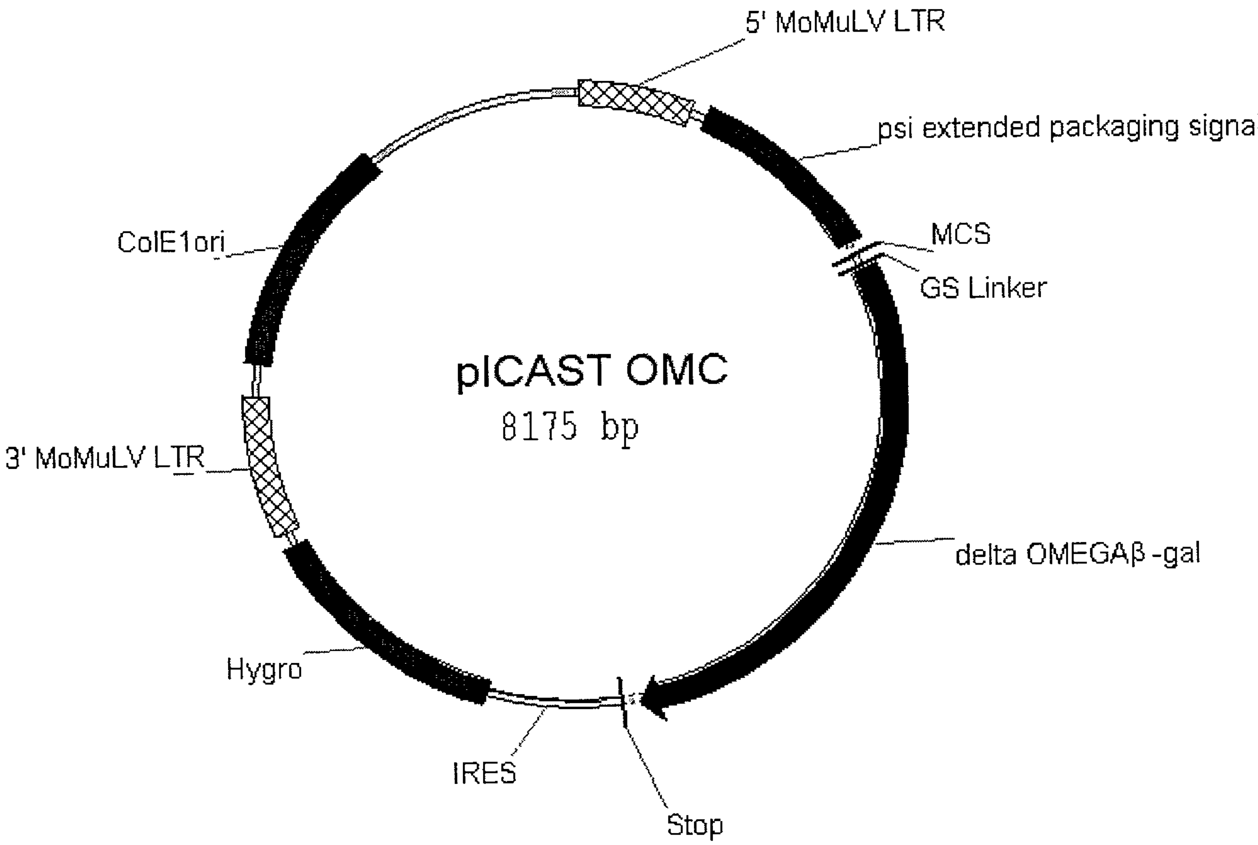
5' MoMuLV LTR
psi extended packaging signal
MCS
GS Linker
ColE1ori
pICAST OMC
8175 bp
3' MoMuLV LTR
delta OMEGAβ -gal
Hygro
IRES
Stop

Figure 12A

```
1    CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG
     GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC
---------------------------------------------------------------------------
51   CCCCGGCTCA GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA
     GGGGCCGAGT CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT
---------------------------------------------------------------------------
101  GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC AAGAACAGAT
     CCTATAGACA CCATTCGTCA AGGACGGGGC CGAGTCCCGG TTCTTGTCTA
---------------------------------------------------------------------------
151  GGTCCCCAGA TGCGGTCCAG CCCTCAGCAG TTTCTAGAGA ACCATCAGAT
     CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC AAAGATCTCT TGGTAGTCTA
---------------------------------------------------------------------------
201  GTTTCCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC TTATTTGAAC
     CAAAGGTCCC ACGGGGTTCC TGGACTTTAC TGGGACACGG AATAAACTTG
---------------------------------------------------------------------------
251  TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA
     ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT
---------------------------------------------------------------------------
301  GCTCAATAAA AGAGCCCACA ACCCCTCACT CGGGGCGCCA GTCCTCCGAT
     CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA
---------------------------------------------------------------------------
351  TGACTGAGTC GCCCGGGTAC CCGTGTATCC AATAAACCCT CTTGCAGTTG
     ACTGACTCAG CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC
---------------------------------------------------------------------------
401  CATCCGACTT GTGGTCTCGC TGTTCCTTGG GAGGGTCTCC TCTGAGTGAT
     GTAGGCTGAA CACCAGAGCG ACAAGGAACC CTCCCAGAGG AGACTCACTA
---------------------------------------------------------------------------
451  TGACTACCCG TCAGCGGGGG TCTTTCATTT GGGGGCTCGT CCGGGATCGG
     ACTGATGGGC AGTCGCCCCC AGAAAGTAAA CCCCCGAGCA GGCCCTAGCC
---------------------------------------------------------------------------
501  GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG CAAGCTGGCC
     CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC GTTCGACCGG
---------------------------------------------------------------------------
551  AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA
     TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGACTAAAAT
---------------------------------------------------------------------------
601  TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC
     ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG
---------------------------------------------------------------------------
651  CGTGGTGGAA CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG
     GCACCACCTT GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC
---------------------------------------------------------------------------
701  TCCCAGGGAC TTTGGGGGCC GTTTTTGTGG CCCGACCTGA GGAAGGGAGT
     AGGGTCCCTG AAACCCCCGG CAAAAACACC GGGCTGGACT CCTTCCCTCA
---------------------------------------------------------------------------
751  CGATGTGGAA TCCGACCCCG TCAGGATATG TGGTTCTGGT AGGAGACGAG
     GCTACACCTT AGGCTGGGGC AGTCCTATAC ACCAAGACCA TCCTCTGCTC
---------------------------------------------------------------------------
801  AACCTAAAAC AGTTCCCGCC TCCGTCTGAA TTTTTGCTTT CGGTTTGGAA
     TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA GCCAAACCTT
---------------------------------------------------------------------------
851  CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT
     GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA
---------------------------------------------------------------------------
901  CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC
     GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG
---------------------------------------------------------------------------
```

FIGURE 12B

```
951   TCCCTTAAGT TTGACCTTAG GTAACTGGAA AGATGTCGAG CGGCTCGCTC
      AGGGAATTCA AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG
-----------------------------------------------------------------------
1001  ACAACCAGTC GGTAGATGTC AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT
      TGTTGGTCAG CCATCTACAG TTCTTCTCTG CAACCCAATG GAAGACGAGA
-----------------------------------------------------------------------
1051  GCAGAATGGC CAACCTTTAA CGTCGGATGG CCGCGAGACG GCACCTTTAA
      CGTCTTACCG GTTGGAAATT GCAGCCTACC GGCGCTCTGC CGTGGAAATT
-----------------------------------------------------------------------
1101  CCGAGACCTC ATCACCCAGG TTAAGATCAA GGTCTTTTCA CCTGGCCCGC
      GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT GGACCGGGCG
-----------------------------------------------------------------------
1151  ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT
      TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA
-----------------------------------------------------------------------
1201  TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC
      AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG
-----------------------------------------------------------------------
1251  TCCTCTTCCT CCATCCGCCC CGTCTCTCCC CCTTGAACCT CCTCGTTCGA
      AGGAGAAGGA GGTAGGCGGG GCAGAGAGGG GGAACTTGGA GGAGCAAGCT
-----------------------------------------------------------------------
1301  CCCCGCCTCG ATCCTCCCTT TATCCAGCCC TCACTCCTTC TCTAGGCGCC
      GGGGCGGAGC TAGGAGGGAA ATAGGTCGGG AGTGAGGAAG AGATCCGCGG
-----------------------------------------------------------------------
1351  GGCCGCTCTA GCCCATTAAT ACGACTCACT ATAGGGCGAT TCGAATCAGG
      CCGGCGAGAT CGGGTAATTA TGCTGAGTGA TATCCCGCTA AGCTTAGTCC
-----------------------------------------------------------------------
1401  CCTTGGCGCG CCGGATCCTT AATTAAGCGC AATTGGGAGG TGGCGGTAGC
      GGAACCGCGC GGCCTAGGAA TTAATTCGCG TTAACCCTCC ACCGCCATCG
-----------------------------------------------------------------------
1451  CTCGAGATGG GCGTGATTAC GGATTCACTG GCCGTCGTTT TACAACGTCG
      GAGCTCTACC CGCACTAATG CCTAAGTGAC CGGCAGCAAA ATGTTGCAGC
-----------------------------------------------------------------------
1501  TGACTGGGAA AACCCTGGCG TTACCCAACT TAATCGCCTT GCAGCACATC
      ACTGACCCTT TTGGGACCGC AATGGGTTGA ATTAGCGGAA CGTCGTGTAG
-----------------------------------------------------------------------
1551  CCCCTTTCGC CAGCTGGCGT AATAGCGAAG AGGCCCGCAC CGATCGCCCT
      GGGGAAAGCG GTCGACCGCA TTATCGCTTC TCCGGGCGTG GCTAGCGGGA
-----------------------------------------------------------------------
1601  TCCCAACAGT TACGCAGCCT GAATGGCGAA TGGCGCTTTG CCTGGTTTCC
      AGGGTTGTCA ATGCGTCGGA CTTACCGCTT ACCGCGAAAC GGACCAAAGG
-----------------------------------------------------------------------
1651  GGCACCAGAA GCGGTGCCGG AAAGCTGGCT GGAGTGCGAT CTTCCTGAGG
      CCGTGGTCTT CGCCACGGCC TTTCGACCGA CCTCACGCTA GAAGGACTCC
-----------------------------------------------------------------------
1701  CCGATACTGT CGTCGTCCCC TCAAACTGGC AGATGCACGG TTACGATGCG
      GGCTATGACA GCAGCAGGGG AGTTTGACCG TCTACGTGCC AATGCTACGC
-----------------------------------------------------------------------
1751  CCCATCTACA CCAACGTGAC CTATCCCATT ACGGTCAATC CGCCGTTTGT
      GGGTAGATGT GGTTGCACTG GATAGGGTAA TGCCAGTTAG GCGGCAAACA
-----------------------------------------------------------------------
1801  TCCCACGGAG AATCCGACGG GTTGTTACTC GCTCACATTT AATGTTGATG
      AGGGTGCCTC TTAGGCTGCC CAACAATGAG CGAGTGTAAA TTACAACTAC
-----------------------------------------------------------------------
1851  AAAGCTGGCT ACAGGAAGGC CAGACGCGAA TTATTTTTGA TGGCGTTAAC
      TTTCGACCGA TGTCCTTCCG GTCTGCGCTT AATAAAAACT ACCGCAATTG
-----------------------------------------------------------------------
```

1901 TCGGCGTTTC ATCTGTGGTG CAACGGGCGC TGGGTCGGTT ACGGCCAGGA
AGCCGCAAAG TAGACACCAC GTTGCCCGCG ACCCAGCCAA TGCCGGTCCT

1951 CAGTCGTTTG CCGTCTGAAT TTGACCTGAG CGCATTTTTA CGCGCCGGAG
GTCAGCAAAC GGCAGACTTA AACTGGACTC GCGTAAAAAT GCGCGGCCTC

2001 AAAACCGCCT CGCGGTGATG GTGCTGCGCT GGAGTGACGG CAGTTATCTG
TTTTGGCGGA GCGCCACTAC CACGACGCGA CCTCACTGCC GTCAATAGAC

2051 GAAGATCAGG ATATGTGGCG GATGAGCGGC ATTTTCCGTG ACGTCTCGTT
CTTCTAGTCC TATACACCGC CTACTCGCCG TAAAAGGCAC TGCAGAGCAA

2101 GCTGCATAAA CCGACTACAC AAATCAGCGA TTTCCATGTT GCCACTCGCT
CGACGTATTT GGCTGATGTG TTTAGTCGCT AAAGGTACAA CGGTGAGCGA

2151 TTAATGATGA TTTCAGCCGC GCTGTACTGG AGGCTGAAGT TCAGATGTGC
AATTACTACT AAAGTCGGCG CGACATGACC TCCGACTTCA AGTCTACACG

2201 GGCGAGTTGC GTGACTACCT ACGGGTAACA GTTTCTTTAT GGCAGGGTGA
CCGCTCAACG CACTGATGGA TGCCCATTGT CAAAGAAATA CCGTCCCACT

2251 AACGCAGGTC GCCAGCGGCA CCGCGCCTTT CGGCGGTGAA ATTATCGATG
TTGCGTCCAG CGGTCGCCGT GGCGCGGAAA GCCGCCACTT TAATAGCTAC

2301 AGCGTGGTGG TTATGCCGAT CGCGTCACAC TACGTCTGAA CGTCGAAAAC
TCGCACCACC AATACGGCTA GCGCAGTGTG ATGCAGACTT GCAGCTTTTG

2351 CCGAAACTGT GGAGCGCCGA AATCCCGAAT CTCTATCGTG CGGTGGTTGA
GGCTTTGACA CCTCGCGGCT TTAGGGCTTA GAGATAGCAC GCCACCAACT

2401 ACTGCACACC GCCGACGGCA CGCTGATTGA AGCAGAAGCC TGCGATGTCG
TGACGTGTGG CGGCTGCCGT GCGACTAACT TCGTCTTCGG ACGCTACAGC

2451 GTTTCCGCGA GGTGCGGATT GAAAATGGTC TGCTGCTGCT GAACGGCAAG
CAAAGGCGCT CCACGCCTAA CTTTTACCAG ACGACGACGA CTTGCCGTTC

2501 CCGTTGCTGA TTCGAGGCGT TAACCGTCAC GAGCATCATC CTCTGCATGG
GGCAACGACT AAGCTCCGCA ATTGGCAGTG CTCGTAGTAG GAGACGTACC

2551 TCAGGTCATG GATGAGCAGA CGATGGTGCA GGATATCCTG CTGATGAAGC
AGTCCAGTAC CTACTCGTCT GCTACCACGT CCTATAGGAC GACTACTTCG

2601 AGAACAACTT TAACGCCGTG CGCTGTTCGC ATTATCCGAA CCATCCGCTG
TCTTGTTGAA ATTGCGGCAC GCGACAAGCG TAATAGGCTT GGTAGGCGAC

2651 TGGTACACGC TGTGCGACCG CTACGGCCTG TATGTGGTGG ATGAAGCCAA
ACCATGTGCG ACACGCTGGC GATGCCGGAC ATACACCACC TACTTCGGTT

2701 TATTGAAACC CACGGCATGG TGCCAATGAA TCGTCTGACC GATGATCCGC
ATAACTTTGG GTGCCGTACC ACGGTTACTT AGCAGACTGG CTACTAGGCG

2751 GCTGGCTACC GGCGATGAGC GAACGCGTAA CGCGAATGGT GCAGCGCGAT
CGACCGATGG CCGCTACTCG CTTGCGCATT GCGCTTACCA CGTCGCGCTA

2801 CGTAATCACC CGAGTGTGAT CATCTGGTCG CTGGGGAATG AATCAGGCCA
GCATTAGTGG GCTCACACTA GTAGACCAGC GACCCCTTAC TTAGTCCGGT

```
2851  CGGCGCTAAT CACGACGCGC TGTATCGCTG GATCAAATCT GTCGATCCTT
      GCCGCGATTA GTGCTGCGCG ACATAGCGAC CTAGTTTAGA CAGCTAGGAA
-------------------------------------------------------------
2901  CCCGCCCGGT GCAGTATGAA GGCGGCGGAG CCGACACCAC GGCCACCGAT
      GGGCGGGCCA CGTCATACTT CCGCCGCCTC GGCTGTGGTG CCGGTGGCTA
-------------------------------------------------------------
2951  ATTATTTGCC CGATGTACGC GCGCGTGGAT GAAGACCAGC CCTTCCCGGC
      TAATAAACGG GCTACATGCG CGCGCACCTA CTTCTGGTCG GGAAGGGCCG
-------------------------------------------------------------
3001  TGTGCCGAAA TGGTCCATCA AAAAATGGCT TTCGCTACCT GGAGAGACGC
      ACACGGCTTT ACCAGGTAGT TTTTTACCGA AAGCGATGGA CCTCTCTGCG
-------------------------------------------------------------
3051  GCCCGCTGAT CCTTTGCGAA TACGCCCACG CGATGGGTAA CAGTCTTGGC
      CGGGCGACTA GGAAACGCTT ATGCGGGTGC GCTACCCATT GTCAGAACCG
-------------------------------------------------------------
3101  GGTTTCGCTA AATACTGGCA GGCGTTTCGT CAGTATCCCC GTTTACAGGG
      CCAAAGCGAT TTATGACCGT CCGCAAAGCA GTCATAGGGG CAAATGTCCC
-------------------------------------------------------------
3151  CGGCTTCGTC TGGGACTGGG TGGATCAGTC GCTGATTAAA TATGATGAAA
      GCCGAAGCAG ACCCTGACCC ACCTAGTCAG CGACTAATTT ATACTACTTT
-------------------------------------------------------------
3201  ACGGCAACCC GTGGTCGGCT TACGGCGGTG ATTTTGGCGA TACGCCGAAC
      TGCCGTTGGG CACCAGCCGA ATGCCGCCAC TAAAACCGCT ATGCGGCTTG
-------------------------------------------------------------
3251  GATCGCCAGT TCTGTATGAA CGGTCTGGTC TTTGCCGACC GCACGCCGCA
      CTAGCGGTCA AGACATACTT GCCAGACCAG AAACGGCTGG CGTGCGGCGT
-------------------------------------------------------------
3301  TCCAGCGCTG ACGGAAGCAA AACACCAGCA GCAGTTTTTC CAGTTCCGTT
      AGGTCGCGAC TGCCTTCGTT TTGTGGTCGT CGTCAAAAAG GTCAAGGCAA
-------------------------------------------------------------
3351  TATCCGGGCA AACCATCGAA GTGACCAGCG AATACCTGTT CCGTCATAGC
      ATAGGCCCGT TTGGTAGCTT CACTGGTCGC TTATGGACAA GGCAGTATCG
-------------------------------------------------------------
3401  GATAACGAGC TCCTGCACTG GATGGTGGCG CTGGATGGTA AGCCGCTGGC
      CTATTGCTCG AGGACGTGAC CTACCACCGC GACCTACCAT TCGGCGACCG
-------------------------------------------------------------
3451  AAGCGGTGAA GTGCCTCTGG ATGTCGCTCC ACAAGGTAAA CAGTTGATTG
      TTCGCCACTT CACGGAGACC TACAGCGAGG TGTTCCATTT GTCAACTAAC
-------------------------------------------------------------
3501  AACTGCCTGA ACTACCGCAG CCGGAGAGCG CCGGGCAACT CTGGCTCACA
      TTGACGGACT TGATGGCGTC GGCCTCTCGC GGCCCGTTGA GACCGAGTGT
-------------------------------------------------------------
3551  GTACGCGTAG TGCAACCGAA CGCGACCGCA TGGTCAGAAG CCGGGCACAT
      CATGCGCATC ACGTTGGCTT GCGCTGGCGT ACCAGTCTTC GGCCCGTGTA
-------------------------------------------------------------
3601  CAGCGCCTGG CAGCAGTGGC GTCTGGCGGA AAACCTCAGT GTGACGCTCC
      GTCGCGGACC GTCGTCACCG CAGACCGCCT TTTGGAGTCA CACTGCGAGG
-------------------------------------------------------------
3651  CCGCCGCGTC CCACGCCATC CCGCATCTGA CCACCAGCGA AATGGATTTT
      GGCGGCGCAG GGTGCGGTAG GGCGTAGACT GGTGGTCGCT TTACCTAAAA
-------------------------------------------------------------
3701  TGCATCGAGC TGGGTAATAA GCGTTGGCAA TTTAACCGCC AGTCAGGCTT
      ACGTAGCTCG ACCCATTATT CGCAACCGTT AAATTGGCGG TCAGTCCGAA
-------------------------------------------------------------
3751  TCTTTCACAG ATGTGGATTG GCGATAAAAA ACAACTGCTG ACGCCGCTGC
      AGAAAGTGTC TACACCTAAC CGCTATTTTT TGTTGACGAC TGCGGCGACG
-------------------------------------------------------------
```

```
3801  GCGATCAGTT CACCCGTGTC GATAGATCTG AACAGAAACT CATTTCCGAA
      CGCTAGTCAA GTGGGCACAG CTATCTAGAC TTGTCTTTGA GTAAAGGCTT
-------------------------------------------------------------
3851  GAAGACCTAG TCGACCATCA TCATCATCAT CACCGGTAAT AATAGGTAGA
      CTTCTGGATC AGCTGGTAGT AGTAGTAGTA GTGGCCATTA TTATCCATCT
-------------------------------------------------------------
3901  TAAGTGACTG ATTAGATGCA TTTCGACTAG ATCCCTCGAC CAATTCCGGT
      ATTCACTGAC TAATCTACGT AAAGCTGATC TAGGGAGCTG GTTAAGGCCA
-------------------------------------------------------------
3951  TATTTTCCAC CATATTGCCG TCTTTTGGCA ATGTGAGGGC CCGGAAACCT
      ATAAAAGGTG GTATAACGGC AGAAAACCGT TACACTCCCG GGCCTTTGGA
-------------------------------------------------------------
4001  GGCCCTGTCT TCTTGACGAG CATTCCTAGG GGTCTTTCCC CTCTCGCCAA
      CCGGGACAGA AGAACTGCTC GTAAGGATCC CCAGAAAGGG GAGAGCGGTT
-------------------------------------------------------------
4051  AGGAATGCAA GGTCTGTTGA ATGTCGTGAA GGAAGCAGTT CCTCTGGAAG
      TCCTTACGTT CCAGACAACT TACAGCACTT CCTTCGTCAA GGAGACCTTC
-------------------------------------------------------------
4101  CTTCTTGAAG ACAAACAACG TCTGTAGCGA CCCTTTGCAG GCAGCGGAAC
      GAAGAACTTC TGTTTGTTGC AGACATCGCT GGGAAACGTC CGTCGCCTTG
-------------------------------------------------------------
4151  CCCCCACCTG GCGACAGGTG CCTCTGCGGC CAAAAGCCAC GTGTATAAGA
      GGGGGTGGAC CGCTGTCCAC GGAGACGCCG GTTTTCGGTG CACATATTCT
-------------------------------------------------------------
4201  TACACCTGCA AAGGCGGCAC AACCCCAGTG CCACGTTGTG AGTTGGATAG
      ATGTGGACGT TTCCGCCGTG TTGGGGTCAC GGTGCAACAC TCAACCTATC
-------------------------------------------------------------
4251  TTGTGGAAAG AGTCAAATGG CTCTCCTCAA GCGTATTCAA CAAGGGGCTG
      AACACCTTTC TCAGTTTACC GAGAGGAGTT CGCATAAGTT GTTCCCCGAC
-------------------------------------------------------------
4301  AAGGATGCCC AGAAGGTACC CCATTGTATG GGATCTGATC TGGGGCCTCG
      TTCCTACGGG TCTTCCATGG GGTAACATAC CCTAGACTAG ACCCCGGAGC
-------------------------------------------------------------
4351  GTGCACATGC TTTACATGTG TTTAGTCGAG GTTAAAAAAC GTCTAGGCCC
      CACGTGTACG AAATGTACAC AAATCAGCTC CAATTTTTTG CAGATCCGGG
-------------------------------------------------------------
4401  CCCGAACCAC GGGGACGTGG TTTTCCTTTG AAAAACACGA TGATAATACC
      GGGCTTGGTG CCCCTGCACC AAAAGGAAAC TTTTTGTGCT ACTATTATGG
-------------------------------------------------------------
4451  ATGAAAAAGC CTGAACTCAC CGCGACGTCT GTCGAGAAGT TTCTGATCGA
      TACTTTTTCG GACTTGAGTG GCGCTGCAGA CAGCTCTTCA AAGACTAGCT
-------------------------------------------------------------
4501  AAAGTTCGAC AGCGTCTCCG ACCTGATGCA GCTCTCGGAG GGCGAAGAAT
      TTTCAAGCTG TCGCAGAGGC TGGACTACGT CGAGAGCCTC CCGCTTCTTA
-------------------------------------------------------------
4551  CTCGTGCTTT CAGCTTCGAT GTAGGAGGGC GTGGATATGT CCTGCGGGTA
      GAGCACGAAA GTCGAAGCTA CATCCTCCCG CACCTATACA GGACGCCCAT
-------------------------------------------------------------
4601  AATAGCTGCG CCGATGGTTT CTACAAAGAT CGTTATGTTT ATCGGCACTT
      TTATCGACGC GGCTACCAAA GATGTTTCTA GCAATACAAA TAGCCGTGAA
-------------------------------------------------------------
4651  TGCATCGGCC GCGCTCCCGA TTCCGGAAGT GCTTGACATT GGGGAATTTA
      ACGTAGCCGG CGCGAGGGCT AAGGCCTTCA CGAACTGTAA CCCCTTAAAT
-------------------------------------------------------------
4701  GCGAGAGCCT GACCTATTGC ATCTCCCGCC GTGCACAGGG TGTCACGTTG
      CGCTCTCGGA CTGGATAACG TAGAGGGCGG CACGTGTCCC ACAGTGCAAC
-------------------------------------------------------------
```

4751 CAAGACCTGC CTGAAACCGA ACTGCCCGCT GTTCTGCAGC CGGTCGCGGA
GTTCTGGACG GACTTTGGCT TGACGGGCGA CAAGACGTCG GCCAGCGCCT

4801 GGCCATGGAT GCGATCGCTG CGGCCGATCT TAGCCAGACG AGCGGGTTCG
CCGGTACCTA CGCTAGCGAC GCCGGCTAGA ATCGGTCTGC TCGCCCAAGC

4851 GCCCATTCGG ACCGCAAGGA ATCGGTCAAT ACACTACATG GCGTGATTTC
CGGGTAAGCC TGGCGTTCCT TAGCCAGTTA TGTGATGTAC CGCACTAAAG

4901 ATATGCGCGA TTGCTGATCC CCATGTGTAT CACTGGCAAA CTGTGATGGA
TATACGCGCT AACGACTAGG GGTACACATA GTGACCGTTT GACACTACCT

4951 CGACACCGTC AGTGCGTCCG TCGCGCAGGC TCTCGATGAG CTGATGCTTT
GCTGTGGCAG TCACGCAGGC AGCGCGTCCG AGAGCTACTC GACTACGAAA

5001 GGGCCGAGGA CTGCCCCGAA GTCCGGCACC TCGTGCACGC GGATTTCGGC
CCCGGCTCCT GACGGGGCTT CAGGCCGTGG AGCACGTGCG CCTAAAGCCG

5051 TCCAACAATG TCCTGACGGA CAATGGCCGC ATAACAGCGG TCATTGACTG
AGGTTGTTAC AGGACTGCCT GTTACCGGCG TATTGTCGCC AGTAACTGAC

5101 GAGCGAGGCG ATGTTCGGGG ATTCCCAATA CGAGGTCGCC AACATCTTCT
CTCGCTCCGC TACAAGCCCC TAAGGGTTAT GCTCCAGCGG TTGTAGAAGA

5151 TCTGGAGGCC GTGGTTGGCT TGTATGGAGC AGCAGACGCG CTACTTCGAG
AGACCTCCGG CACCAACCGA ACATACCTCG TCGTCTGCGC GATGAAGCTC

5201 CGGAGGCATC CGGAGCTTGC AGGATCGCCG CGGCTCCGGG CGTATATGCT
GCCTCCGTAG GCCTCGAACG TCCTAGCGGC GCCGAGGCCC GCATATACGA

5251 CCGCATTGGT CTTGACCAAC TCTATCAGAG CTTGGTTGAC GGCAATTTCG
GGCGTAACCA GAACTGGTTG AGATAGTCTC GAACCAACTG CCGTTAAAGC

5301 ATGATGCAGC TTGGGCGCAG GGTCGATGCG ACGCAATCGT CCGATCCGGA
TACTACGTCG AACCCGCGTC CCAGCTACGC TGCGTTAGCA GGCTAGGCCT

5351 GCCGGGACTG TCGGGCGTAC ACAAATCGCC CGCAGAAGCG CGGCCGTCTG
CGGCCCTGAC AGCCCGCATG TGTTTAGCGG GCGTCTTCGC GCCGGCAGAC

5401 GACCGATGGC TGTGTAGAAG TACTCGCCGA TAGTGGAAAC CGACGCCCCA
CTGGCTACCG ACACATCTTC ATGAGCGGCT ATCACCTTTG GCTGCGGGGT

5451 GCACTCGTCC GAGGGCAAAG GAATAGAGTA GATGCCGACC GGGATCTATC
CGTGAGCAGG CTCCCGTTTC CTTATCTCAT CTACGGCTGG CCCTAGATAG

5501 GATAAAATAA AAGATTTTAT TTAGTCTCCA GAAAAAGGGG GGAATGAAAG
CTATTTTATT TTCTAAAATA AATCAGAGGT CTTTTTCCCC CCTTACTTTC

5551 ACCCCACCTG TAGGTTTGGC AAGCTAGCTT AAGTAACGCC ATTTTGCAAG
TGGGGTGGAC ATCCAAACCG TTCGATCGAA TTCATTGCGG TAAAACGTTC

5601 GCATGGAAAA ATACATAACT GAGAATAGAG AAGTTCAGAT CAAGGTCAGG
CGTACCTTTT TATGTATTGA CTCTTATCTC TTCAAGTCTA GTTCCAGTCC

5651 AACAGATGGA ACAGCTGAAT ATGGGCCAAA CAGGATATCT GTGGTAAGCA
TTGTCTACCT TGTCGACTTA TACCCGGTTT GTCCTATAGA CACCATTCGT

```
5701  GTTCCTGCCC CGGCTCAGGG CCAAGAACAG ATGGAACAGC TGAATATGGG
      CAAGGACGGG GCCGAGTCCC GGTTCTTGTC TACCTTGTCG ACTTATACCC

5751  CCAAACAGGA TATCTGTGGT AAGCAGTTCC TGCCCCGGCT CAGGGCCAAG
      GGTTTGTCCT ATAGACACCA TTCGTCAAGG ACGGGGCCGA GTCCCGGTTC

5801  AACAGATGGT CCCCAGATGC GGTCCAGCCC TCAGCAGTTT CTAGAGAACC
      TTGTCTACCA GGGGTCTACG CCAGGTCGGG AGTCGTCAAA GATCTCTTGG

5851  ATCAGATGTT TCCAGGGTGC CCCAAGGACC TGAAATGACC CTGTGCCTTA
      TAGTCTACAA AGGTCCCACG GGGTTCCTGG ACTTTACTGG GACACGGAAT

5901  TTTGAACTAA CCAATCAGTT CGCTTCTCGC TTCTGTTCGC GCGCTTCTGC
      AAACTTGATT GGTTAGTCAA GCGAAGAGCG AAGACAAGCG CGCGAAGACG

5951  TCCCCGAGCT CAATAAAAGA GCCCACAACC CCTCACTCGG GGCGCCAGTC
      AGGGGCTCGA GTTATTTTCT CGGGTGTTGG GGAGTGAGCC CCGCGGTCAG

6001  CTCCGATTGA CTGAGTCGCC CGGGTACCCG TGTATCCAAT AAACCCTCTT
      GAGGCTAACT GACTCAGCGG GCCCATGGGC ACATAGGTTA TTTGGGAGAA

6051  GCAGTTGCAT CCGACTTGTG GTCTCGCTGT TCCTTGGGAG GGTCTCCTCT
      CGTCAACGTA GGCTGAACAC CAGAGCGACA AGGAACCCTC CCAGAGGAGA

6101  GAGTGATTGA CTACCCGTCA GCGGGGGTCT TTCATTCATG CAGCATGTAT
      CTCACTAACT GATGGGCAGT CGCCCCCAGA AAGTAAGTAC GTCGTACATA

6151  CAAAATTAAT TTGGTTTTTT TTCTTAAGTA TTTACATTAA ATGGCCATAG
      GTTTTAATTA AACCAAAAAA AAGAATTCAT AAATGTAATT TACCGGTATC

6201  TTGCATTAAT GAATCGGCCA ACGCGCGGGG AGAGGCGGTT TGCGTATTGG
      AACGTAATTA CTTAGCCGGT TGCGCGCCCC TCTCCGCCAA ACGCATAACC

6251  CGCTCTTCCG CTTCCTCGCT CACTGACTCG CTGCGCTCGG TCGTTCGGCT
      GCGAGAAGGC GAAGGAGCGA GTGACTGAGC GACGCGAGCC AGCAAGCCGA

6301  GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG TTATCCACAG
      CGCCGCTCGC CATAGTCGAG TGAGTTTCCG CCATTATGCC AATAGGTGTC

6351  AATCAGGGGA TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG
      TTAGTCCCCT ATTGCGTCCT TTCTTGTACA CTCGTTTTCC GGTCGTTTTC

6401  GCCAGGAACC GTAAAAAGGC CGCGTTGCTG GCGTTTTTCC ATAGGCTCCG
      CGGTCCTTGG CATTTTTCCG GCGCAACGAC CGCAAAAAGG TATCCGAGGC

6451  CCCCCCTGAC GAGCATCACA AAAATCGACG CTCAAGTCAG AGGTGGCGAA
      GGGGGGACTG CTCGTAGTGT TTTTAGCTGC GAGTTCAGTC TCCACCGCTT

6501  ACCCGACAGG ACTATAAAGA TACCAGGCGT TTCCCCCTGG AAGCTCCCTC
      TGGGCTGTCC TGATATTTCT ATGGTCCGCA AAGGGGGACC TTCGAGGGAG

6551  GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC TGTCCGCCTT
      CACGCGAGAG GACAAGGCTG GGACGGCGAA TGGCCTATGG ACAGGCGGAA

6601  TCTCCCTTCG GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC
      AGAGGGAAGC CCTTCGCACC GCGAAAGAGT ATCGAGTGCG ACATCCATAG
```

```
6651  TCAGTTCGGT GTAGGTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC
      AGTCAAGCCA CATCCAGCAA GCGAGGTTCG ACCCGACACA CGTGCTTGGG
-----------------------------------------------------------
6701  CCCGTTCAGC CCGACCGCTG CGCCTTATCC GGTAACTATC GTCTTGAGTC
      GGGCAAGTCG GGCTGGCGAC GCGGAATAGG CCATTGATAG CAGAACTCAG
-----------------------------------------------------------
6751  CAACCCGGTA AGACACGACT TATCGCCACT GGCAGCAGCC ACTGGTAACA
      GTTGGGCCAT TCTGTGCTGA ATAGCGGTGA CCGTCGTCGG TGACCATTGT
-----------------------------------------------------------
6801  GGATTAGCAG AGCGAGGTAT GTAGGCGGTG CTACAGAGTT CTTGAAGTGG
      CCTAATCGTC TCGCTCCATA CATCCGCCAC GATGTCTCAA GAACTTCACC
-----------------------------------------------------------
6851  TGGCCTAACT ACGGCTACAC TAGAAGAACA GTATTTGGTA TCTGCGCTCT
      ACCGGATTGA TGCCGATGTG ATCTTCTTGT CATAAACCAT AGACGCGAGA
-----------------------------------------------------------
6901  GCTGAAGCCA GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA
      CGACTTCGGT CAATGGAAGC CTTTTTCTCA ACCATCGAGA ACTAGGCCGT
-----------------------------------------------------------
6951  AACAAACCAC CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT
      TTGTTTGGTG GCGACCATCG CCACCAAAAA AACAAACGTT CGTCGTCTAA
-----------------------------------------------------------
7001  ACGCGCAGAA AAAAAGGATC TCAAGAAGAT CCTTTGATCT TTTCTACGGG
      TGCGCGTCTT TTTTTCCTAG AGTTCTTCTA GGAAACTAGA AAAGATGCCC
-----------------------------------------------------------
7051  GTCTGACGCT CAGTGGAACG AAAACTCACG TTAAGGGATT TTGGTCATGA
      CAGACTGCGA GTCACCTTGC TTTTGAGTGC AATTCCCTAA AACCAGTACT
-----------------------------------------------------------
7101  GATTATCAAA AAGGATCTTC ACCTAGATCC TTTTAAATTA AAAATGAAGT
      CTAATAGTTT TTCCTAGAAG TGGATCTAGG AAAATTTAAT TTTTACTTCA
-----------------------------------------------------------
7151  TTGCGGCCGC AAATCAATCT AAAGTATATA TGAGTAAACT TGGTCTGACA
      AACGCCGGCG TTTAGTTAGA TTTCATATAT ACTCATTTGA ACCAGACTGT
-----------------------------------------------------------
7201  GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT CTGTCTATTT
      CAATGGTTAC GAATTAGTCA CTCCGTGGAT AGAGTCGCTA GACAGATAAA
-----------------------------------------------------------
7251  CGTTCATCCA TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG
      GCAAGTAGGT ATCAACGGAC TGAGGGGCAG CACATCTATT GATGCTATGC
-----------------------------------------------------------
7301  GGAGGGCTTA CCATCTGGCC CCAGTGCTGC AATGATACCG CGAGACCCAC
      CCTCCCGAAT GGTAGACCGG GGTCACGACG TTACTATGGC GCTCTGGGTG
-----------------------------------------------------------
7351  GCTCACCGGC TCCAGATTTA TCAGCAATAA ACCAGCCAGC CGGAAGGGCC
      CGAGTGGCCG AGGTCTAAAT AGTCGTTATT TGGTCGGTCG GCCTTCCCGG
-----------------------------------------------------------
7401  GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC AGTCTATTAA
      CTCGCGTCTT CACCAGGACG TTGAAATAGG CGGAGGTAGG TCAGATAATT
-----------------------------------------------------------
7451  TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA
      AACAACGGCC CTTCGATCTC ATTCATCAAG CGGTCAATTA TCAAACGCGT
-----------------------------------------------------------
7501  ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT
      TGCAACAACG GTAACGATGT CCGTAGCACC ACAGTGCGAG CAGCAAACCA
-----------------------------------------------------------
7551  ATGGCTTCAT TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC
      TACCGAAGTA AGTCGAGGCC AAGGGTTGCT AGTTCCGCTC AATGTACTAG
-----------------------------------------------------------
```

```
7601  CCCCATGTTG TGCAAAAAAG CGGTTAGCTC CTTCGGTCCT CCGATCGTTG
      GGGGTACAAC ACGTTTTTTC GCCAATCGAG GAAGCCAGGA GGCTAGCAAC
----------------------------------------------------------------------------
7651  TCAGAAGTAA GTTGGCCGCA GTGTTATCAC TCATGGTTAT GGCAGCACTG
      AGTCTTCATT CAACCGGCGT CACAATAGTG AGTACCAATA CCGTCGTGAC
----------------------------------------------------------------------------
7701  CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT CTGTGACTGG
      GTATTAAGAG AATGACAGTA CGGTAGGCAT TCTACGAAAA GACACTGACC
----------------------------------------------------------------------------
7751  TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT
      ACTCATGAGT TGGTTCAGTA AGACTCTTAT CACATACGCC GCTGGCTCAA
----------------------------------------------------------------------------
7801  GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT
      CGAGAACGGG CCGCAGTTAT GCCCTATTAT GGCGCGGTGT ATCGTCTTGA
----------------------------------------------------------------------------
7851  TTAAAAGTGC TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG
      AATTTTCACG AGTAGTAACC TTTTGCAAGA AGCCCCGCTT TTGAGAGTTC
----------------------------------------------------------------------------
7901  GATCTTACCG CTGTTGAGAT CCAGTTCGAT GTAACCCACT CGTGCACCCA
      CTAGAATGGC GACAACTCTA GGTCAAGCTA CATTGGGTGA GCACGTGGGT
----------------------------------------------------------------------------
7951  ACTGATCTTC AGCATCTTTT ACTTTCACCA GCGTTTCTGG GTGAGCAAAA
      TGACTAGAAG TCGTAGAAAA TGAAAGTGGT CGCAAAGACC CACTCGTTTT
----------------------------------------------------------------------------
8001  ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA CACGGAAATG
      TGTCCTTCCG TTTTACGGCG TTTTTTCCCT TATTCCCGCT GTGCCTTTAC
----------------------------------------------------------------------------
8051  TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG
      AACTTATGAG TATGAGAAGG AAAAAGTTAT AATAACTTCG TAAATAGTCC
----------------------------------------------------------------------------
8101  GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA
      CAATAACAGA GTACTCGCCT ATGTATAAAC TTACATAAAT CTTTTTATTT
----------------------------------------------------------------------------
8151  CAAATAGGGG TTCCGCGCAC ATTTC
      GTTTATCCCC AAGGCGCGTG TAAAG
----------------------------------------------------------------------------
```

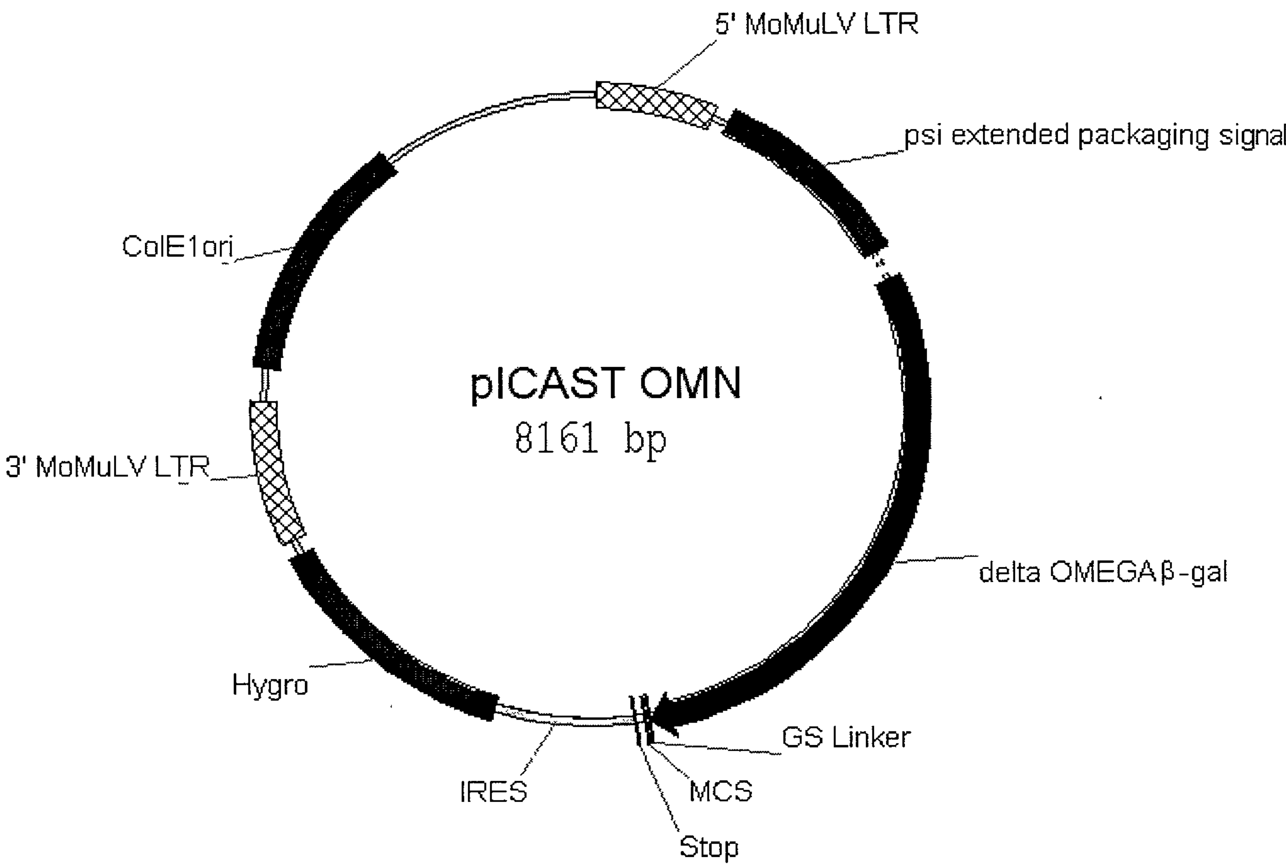
5' MoMuLV LTR
psi extended packaging signal
ColE1ori
pICAST OMN
8161 bp
3' MoMuLV LTR
delta OMEGAβ-gal
Hygro
GS Linker
IRES
MCS
Stop

Figure 13A

```
  1 CTGCAGCCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG
    GACGTCGGAC TTATACCCGG TTTGTCCTAT AGACACCATT CGTCAAGGAC
-------------------------------------------------------------
 51 CCCCGGCTCA GGGCCAAGAA CAGATGGAAC AGCTGAATAT GGGCCAAACA
    GGGGCCGAGT CCCGGTTCTT GTCTACCTTG TCGACTTATA CCCGGTTTGT
-------------------------------------------------------------
101 GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC AAGAACAGAT
    CCTATAGACA CCATTCGTCA AGGACGGGGC CGAGTCCCGG TTCTTGTCTA
-------------------------------------------------------------
151 GGTCCCCAGA TGCGGTCCAG CCCTCAGCAG TTTCTAGAGA ACCATCAGAT
    CCAGGGGTCT ACGCCAGGTC GGGAGTCGTC AAAGATCTCT TGGTAGTCTA
-------------------------------------------------------------
201 GTTTCCAGGG TGCCCCAAGG ACCTGAAATG ACCCTGTGCC TTATTTGAAC
    CAAAGGTCCC ACGGGGTTCC TGGACTTTAC TGGGACACGG AATAAACTTG
-------------------------------------------------------------
251 TAACCAATCA GTTCGCTTCT CGCTTCTGTT CGCGCGCTTC TGCTCCCCGA
    ATTGGTTAGT CAAGCGAAGA GCGAAGACAA GCGCGCGAAG ACGAGGGGCT
-------------------------------------------------------------
301 GCTCAATAAA AGAGCCCACA ACCCCTCACT CGGGGCGCCA GTCCTCCGAT
    CGAGTTATTT TCTCGGGTGT TGGGGAGTGA GCCCCGCGGT CAGGAGGCTA
-------------------------------------------------------------
351 TGACTGAGTC GCCCGGGTAC CCGTGTATCC AATAAACCCT CTTGCAGTTG
    ACTGACTCAG CGGGCCCATG GGCACATAGG TTATTTGGGA GAACGTCAAC
-------------------------------------------------------------
401 CATCCGACTT GTGGTCTCGC TGTTCCTTGG GAGGGTCTCC TCTGAGTGAT
    GTAGGCTGAA CACCAGAGCG ACAAGGAACC CTCCCAGAGG AGACTCACTA
-------------------------------------------------------------
451 TGACTACCCG TCAGCGGGGG TCTTTCATTT GGGGGCTCGT CCGGGATCGG
    ACTGATGGGC AGTCGCCCCC AGAAAGTAAA CCCCCGAGCA GGCCCTAGCC
-------------------------------------------------------------
501 GAGACCCCTG CCCAGGGACC ACCGACCCAC CACCGGGAGG CAAGCTGGCC
    CTCTGGGGAC GGGTCCCTGG TGGCTGGGTG GTGGCCCTCC GTTCGACCGG
-------------------------------------------------------------
551 AGCAACTTAT CTGTGTCTGT CCGATTGTCT AGTGTCTATG ACTGATTTTA
    TCGTTGAATA GACACAGACA GGCTAACAGA TCACAGATAC TGACTAAAAT
-------------------------------------------------------------
601 TGCGCCTGCG TCGGTACTAG TTAGCTAACT AGCTCTGTAT CTGGCGGACC
    ACGCGGACGC AGCCATGATC AATCGATTGA TCGAGACATA GACCGCCTGG
-------------------------------------------------------------
651 CGTGGTGGAA CTGACGAGTT CTGAACACCC GGCCGCAACC CTGGGAGACG
    GCACCACCTT GACTGCTCAA GACTTGTGGG CCGGCGTTGG GACCCTCTGC
-------------------------------------------------------------
701 TCCCAGGGAC TTTGGGGGCC GTTTTTGTGG CCCGACCTGA GGAAGGGAGT
    AGGGTCCCTG AAACCCCCGG CAAAAACACC GGGCTGGACT CCTTCCCTCA
-------------------------------------------------------------
751 CGATGTGGAA TCCGACCCCG TCAGGATATG TGGTTCTGGT AGGAGACGAG
    GCTACACCTT AGGCTGGGGC AGTCCTATAC ACCAAGACCA TCCTCTGCTC
-------------------------------------------------------------
801 AACCTAAAAC AGTTCCCGCC TCCGTCTGAA TTTTTGCTTT CGGTTTGGAA
    TTGGATTTTG TCAAGGGCGG AGGCAGACTT AAAAACGAAA GCCAAACCTT
-------------------------------------------------------------
851 CCGAAGCCGC GCGTCTTGTC TGCTGCAGCA TCGTTCTGTG TTGTCTCTGT
    GGCTTCGGCG CGCAGAACAG ACGACGTCGT AGCAAGACAC AACAGAGACA
-------------------------------------------------------------
901 CTGACTGTGT TTCTGTATTT GTCTGAAAAT TAGGGCCAGA CTGTTACCAC
    GACTGACACA AAGACATAAA CAGACTTTTA ATCCCGGTCT GACAATGGTG
-------------------------------------------------------------
```

FIGURE 13B

```
951  TCCCTTAAGT TTGACCTTAG GTAACTGGAA AGATGTCGAG CGGCTCGCTC
     AGGGAATTCA AACTGGAATC CATTGACCTT TCTACAGCTC GCCGAGCGAG
------------------------------------------------------------------------
1001 ACAACCAGTC GGTAGATGTC AAGAAGAGAC GTTGGGTTAC CTTCTGCTCT
     TGTTGGTCAG CCATCTACAG TTCTTCTCTG CAACCCAATG GAAGACGAGA
------------------------------------------------------------------------
1051 GCAGAATGGC CAACCTTTAA CGTCGGATGG CCGCGAGACG GCACCTTTAA
     CGTCTTACCG GTTGGAAATT GCAGCCTACC GGCGCTCTGC CGTGGAAATT
------------------------------------------------------------------------
1101 CCGAGACCTC ATCACCCAGG TTAAGATCAA GGTCTTTTCA CCTGGCCCGC
     GGCTCTGGAG TAGTGGGTCC AATTCTAGTT CCAGAAAAGT GGACCGGGCG
------------------------------------------------------------------------
1151 ATGGACACCC AGACCAGGTC CCCTACATCG TGACCTGGGA AGCCTTGGCT
     TACCTGTGGG TCTGGTCCAG GGGATGTAGC ACTGGACCCT TCGGAACCGA
------------------------------------------------------------------------
1201 TTTGACCCCC CTCCCTGGGT CAAGCCCTTT GTACACCCTA AGCCTCCGCC
     AAACTGGGGG GAGGGACCCA GTTCGGGAAA CATGTGGGAT TCGGAGGCGG
------------------------------------------------------------------------
1251 TCCTCTTCCT CCATCCGCCC CGTCTCTCCC CCTTGAACCT CCTCGTTCGA
     AGGAGAAGGA GGTAGGCGGG GCAGAGAGGG GGAACTTGGA GGAGCAAGCT
------------------------------------------------------------------------
1301 CCCCGCCTCG ATCCTCCCTT TATCCAGCCC TCACTCCTTC TCTAGGCGCC
     GGGGCGGAGC TAGGAGGGAA ATAGGTCGGG AGTGAGGAAG AGATCCGCGG
------------------------------------------------------------------------
1351 GGCCGCTCTA GCCCATTAAT ACGACTCACT ATAGGGCGAT TCGAACACCA
     CCGGCGAGAT CGGGTAATTA TGCTGAGTGA TATCCCGCTA AGCTTGTGGT
------------------------------------------------------------------------
1401 TGCACCATCA TCATCATCAC GTCGACGAAC AGAAACTCAT TTCCGAAGAA
     ACGTGGTAGT AGTAGTAGTG CAGCTGCTTG TCTTTGAGTA AAGGCTTCTT
------------------------------------------------------------------------
1451 GACCTACTCG AGATGGGCGT GATTACGGAT TCACTGGCCG TCGTTTTACA
     CTGGATGAGC TCTACCCGCA CTAATGCCTA AGTGACCGGC AGCAAAATGT
------------------------------------------------------------------------
1501 ACGTCGTGAC TGGGAAAACC CTGGCGTTAC CCAACTTAAT CGCCTTGCAG
     TGCAGCACTG ACCCTTTTGG GACCGCAATG GGTTGAATTA GCGGAACGTC
------------------------------------------------------------------------
1551 CACATCCCCC TTTCGCCAGC TGGCGTAATA GCGAAGAGGC CCGCACCGAT
     GTGTAGGGGG AAAGCGGTCG ACCGCATTAT CGCTTCTCCG GGCGTGGCTA
------------------------------------------------------------------------
1601 CGCCCTTCCC AACAGTTACG CAGCCTGAAT GGCGAATGGC GCTTTGCCTG
     GCGGGAAGGG TTGTCAATGC GTCGGACTTA CCGCTTACCG CGAAACGGAC
------------------------------------------------------------------------
1651 GTTTCCGGCA CCAGAAGCGG TGCCGGAAAG CTGGCTGGAG TGCGATCTTC
     CAAAGGCCGT GGTCTTCGCC ACGGCCTTTC GACCGACCTC ACGCTAGAAG
------------------------------------------------------------------------
1701 CTGAGGCCGA TACTGTCGTC GTCCCCTCAA ACTGGCAGAT GCACGGTTAC
     GACTCCGGCT ATGACAGCAG CAGGGGAGTT TGACCGTCTA CGTGCCAATG
------------------------------------------------------------------------
1751 GATGCGCCCA TCTACACCAA CGTGACCTAT CCCATTACGG TCAATCCGCC
     CTACGCGGGT AGATGTGGTT GCACTGGATA GGGTAATGCC AGTTAGGCGG
------------------------------------------------------------------------
1801 GTTTGTTCCC ACGGAGAATC CGACGGGTTG TTACTCGCTC ACATTTAATG
     CAAACAAGGG TGCCTCTTAG GCTGCCCAAC AATGAGCGAG TGTAAATTAC
------------------------------------------------------------------------
1851 TTGATGAAAG CTGGCTACAG GAAGGCCAGA CGCGAATTAT TTTTGATGGC
     AACTACTTTC GACCGATGTC CTTCCGGTCT GCGCTTAATA AAAACTACCG
------------------------------------------------------------------------
```

```
1901  GTTAACTCGG CGTTTCATCT GTGGTGCAAC GGGCGCTGGG TCGGTTACGG
      CAATTGAGCC GCAAAGTAGA CACCACGTTG CCCGCGACCC AGCCAATGCC
---------------------------------------------------------------------------
1951  CCAGGACAGT CGTTTGCCGT CTGAATTTGA CCTGAGCGCA TTTTTACGCG
      GGTCCTGTCA GCAAACGGCA GACTTAAACT GGACTCGCGT AAAAATGCGC
---------------------------------------------------------------------------
2001  CCGGAGAAAA CCGCCTCGCG GTGATGGTGC TGCGCTGGAG TGACGGCAGT
      GGCCTCTTTT GGCGGAGCGC CACTACCACG ACGCGACCTC ACTGCCGTCA
---------------------------------------------------------------------------
2051  TATCTGGAAG ATCAGGATAT GTGGCGGATG AGCGGCATTT TCCGTGACGT
      ATAGACCTTC TAGTCCTATA CACCGCCTAC TCGCCGTAAA AGGCACTGCA
---------------------------------------------------------------------------
2101  CTCGTTGCTG CATAAACCGA CTACACAAAT CAGCGATTTC CATGTTGCCA
      GAGCAACGAC GTATTTGGCT GATGTGTTTA GTCGCTAAAG GTACAACGGT
---------------------------------------------------------------------------
2151  CTCGCTTTAA TGATGATTTC AGCCGCGCTG TACTGGAGGC TGAAGTTCAG
      GAGCGAAATT ACTACTAAAG TCGGCGCGAC ATGACCTCCG ACTTCAAGTC
---------------------------------------------------------------------------
2201  ATGTGCGGCG AGTTGCGTGA CTACCTACGG GTAACAGTTT CTTTATGGCA
      TACACGCCGC TCAACGCACT GATGGATGCC CATTGTCAAA GAAATACCGT
---------------------------------------------------------------------------
2251  GGGTGAAACG CAGGTCGCCA GCGGCACCGC GCCTTTCGGC GGTGAAATTA
      CCCACTTTGC GTCCAGCGGT CGCCGTGGCG CGGAAAGCCG CCACTTTAAT
---------------------------------------------------------------------------
2301  TCGATGAGCG TGGTGGTTAT GCCGATCGCG TCACACTACG TCTGAACGTC
      AGCTACTCGC ACCACCAATA CGGCTAGCGC AGTGTGATGC AGACTTGCAG
---------------------------------------------------------------------------
2351  GAAAACCCGA AACTGTGGAG CGCCGAAATC CCGAATCTCT ATCGTGCGGT
      CTTTTGGGCT TTGACACCTC GCGGCTTTAG GGCTTAGAGA TAGCACGCCA
---------------------------------------------------------------------------
2401  GGTTGAACTG CACACCGCCG ACGGCACGCT GATTGAAGCA GAAGCCTGCG
      CCAACTTGAC GTGTGGCGGC TGCCGTGCGA CTAACTTCGT CTTCGGACGC
---------------------------------------------------------------------------
2451  ATGTCGGTTT CCGCGAGGTG CGGATTGAAA ATGGTCTGCT GCTGCTGAAC
      TACAGCCAAA GGCGCTCCAC GCCTAACTTT TACCAGACGA CGACGACTTG
---------------------------------------------------------------------------
2501  GGCAAGCCGT TGCTGATTCG AGGCGTTAAC CGTCACGAGC ATCATCCTCT
      CCGTTCGGCA ACGACTAAGC TCCGCAATTG GCAGTGCTCG TAGTAGGAGA
---------------------------------------------------------------------------
2551  GCATGGTCAG GTCATGGATG AGCAGACGAT GGTGCAGGAT ATCCTGCTGA
      CGTACCAGTC CAGTACCTAC TCGTCTGCTA CCACGTCCTA TAGGACGACT
---------------------------------------------------------------------------
2601  TGAAGCAGAA CAACTTTAAC GCCGTGCGCT GTTCGCATTA TCCGAACCAT
      ACTTCGTCTT GTTGAAATTG CGGCACGCGA CAAGCGTAAT AGGCTTGGTA
---------------------------------------------------------------------------
2651  CCGCTGTGGT ACACGCTGTG CGACCGCTAC GGCCTGTATG TGGTGGATGA
      GGCGACACCA TGTGCGACAC GCTGGCGATG CCGGACATAC ACCACCTACT
---------------------------------------------------------------------------
2701  AGCCAATATT GAAACCCACG GCATGGTGCC AATGAATCGT CTGACCGATG
      TCGGTTATAA CTTTGGGTGC CGTACCACGG TTACTTAGCA GACTGGCTAC
---------------------------------------------------------------------------
2751  ATCCGCGCTG GCTACCGGCG ATGAGCGAAC GCGTAACGCG AATGGTGCAG
      TAGGCGCGAC CGATGGCCGC TACTCGCTTG CGCATTGCGC TTACCACGTC
---------------------------------------------------------------------------
2801  CGCGATCGTA ATCACCCGAG TGTGATCATC TGGTCGCTGG GGAATGAATC
      GCGCTAGCAT TAGTGGGCTC ACACTAGTAG ACCAGCGACC CCTTACTTAG
---------------------------------------------------------------------------
```

2851 AGGCCACGGC GCTAATCACG ACGCGCTGTA TCGCTGGATC AAATCTGTCG
TCCGGTGCCG CGATTAGTGC TGCGCGACAT AGCGACCTAG TTTAGACAGC

2901 ATCCTTCCCG CCCGGTGCAG TATGAAGGCG GCGGAGCCGA CACCACGGCC
TAGGAAGGGC GGGCCACGTC ATACTTCCGC CGCCTCGGCT GTGGTGCCGG

2951 ACCGATATTA TTTGCCCGAT GTACGCGCGC GTGGATGAAG ACCAGCCCTT
TGGCTATAAT AAACGGGCTA CATGCGCGCG CACCTACTTC TGGTCGGGAA

3001 CCCGGCTGTG CCGAAATGGT CCATCAAAAA ATGGCTTTCG CTACCTGGAG
GGGCCGACAC GGCTTTACCA GGTAGTTTTT TACCGAAAGC GATGGACCTC

3051 AGACGCGCCC GCTGATCCTT TGCGAATACG CCCACGCGAT GGGTAACAGT
TCTGCGCGGG CGACTAGGAA ACGCTTATGC GGGTGCGCTA CCCATTGTCA

3101 CTTGGCGGTT TCGCTAAATA CTGGCAGGCG TTTCGTCAGT ATCCCCGTTT
GAACCGCCAA AGCGATTTAT GACCGTCCGC AAAGCAGTCA TAGGGGCAAA

3151 ACAGGGCGGC TTCGTCTGGG ACTGGGTGGA TCAGTCGCTG ATTAAATATG
TGTCCCGCCG AAGCAGACCC TGACCCACCT AGTCAGCGAC TAATTTATAC

3201 ATGAAAACGG CAACCCGTGG TCGGCTTACG GCGGTGATTT TGGCGATACG
TACTTTTGCC GTTGGGCACC AGCCGAATGC CGCCACTAAA ACCGCTATGC

3251 CCGAACGATC GCCAGTTCTG TATGAACGGT CTGGTCTTTG CCGACCGCAC
GGCTTGCTAG CGGTCAAGAC ATACTTGCCA GACCAGAAAC GGCTGGCGTG

3301 GCCGCATCCA GCGCTGACGG AAGCAAAACA CCAGCAGCAG TTTTTCCAGT
CGGCGTAGGT CGCGACTGCC TTCGTTTTGT GGTCGTCGTC AAAAAGGTCA

3351 TCCGTTTATC CGGGCAAACC ATCGAAGTGA CCAGCGAATA CCTGTTCCGT
AGGCAAATAG GCCCGTTTGG TAGCTTCACT GGTCGCTTAT GGACAAGGCA

3401 CATAGCGATA ACGAGCTCCT GCACTGGATG GTGGCGCTGG ATGGTAAGCC
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3451 GCTGGCAAGC GGTGAAGTGC CTCTGGATGT CGCTCCACAA GGTAAACAGT
CGACCGTTCG CCACTTCACG GAGACCTACA GCGAGGTGTT CCATTTGTCA

3501 TGATTGAACT GCCTGAACTA CCGCAGCCGG AGAGCGCCGG GCAACTCTGG
ACTAACTTGA CGGACTTGAT GGCGTCGGCC TCTCGCGGCC CGTTGAGACC

3551 CTCACAGTAC GCGTAGTGCA ACCGAACGCG ACCGCATGGT CAGAAGCCGG
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3651 CGCTCCCCGC CGCGTCCCAC GCCATCCCGC ATCTGACCAC CAGCGAAATG
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      CGGGGGGCTT GGTGCCCCTG CACCAAAAGG AAACTTTTTG TGCTACTATT
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      ATGGTACTTT TTCGGACTTG AGTGGCGCTG CAGACAGCTC TTCAAAGACT
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      AGCTTTTCAA GCTGTCGCAG AGGCTGGACT ACGTCGAGAG CCTCCCGCTT
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```

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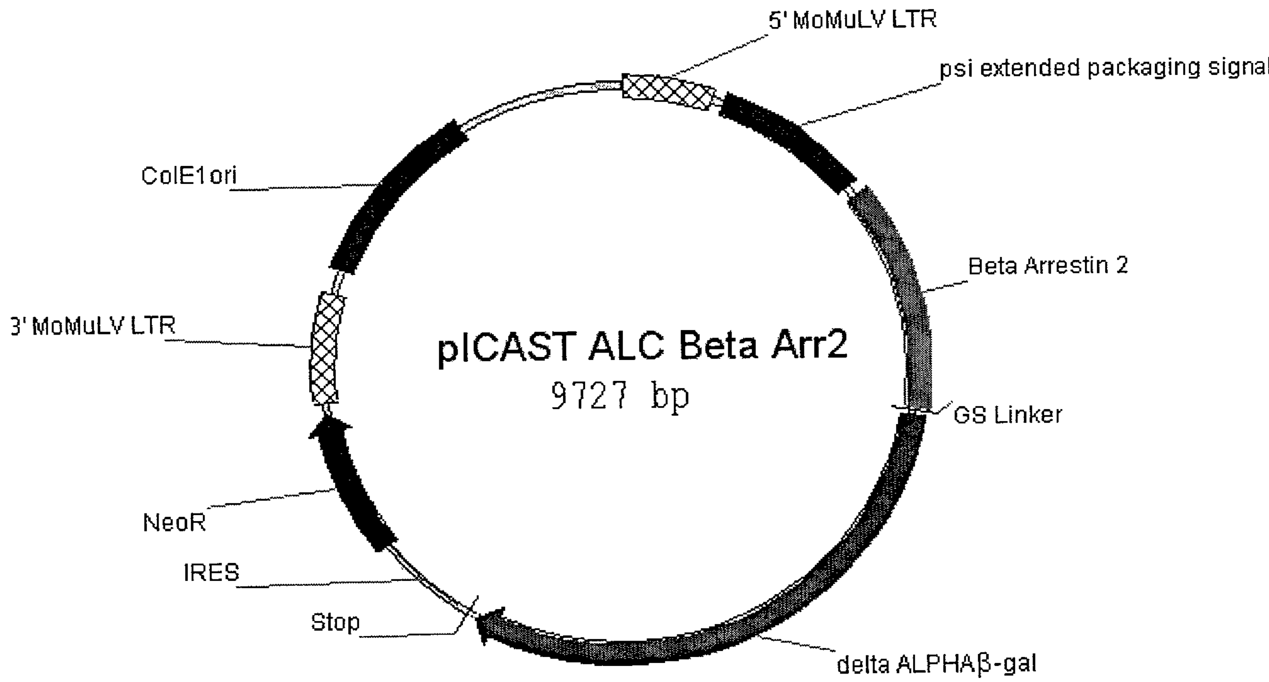
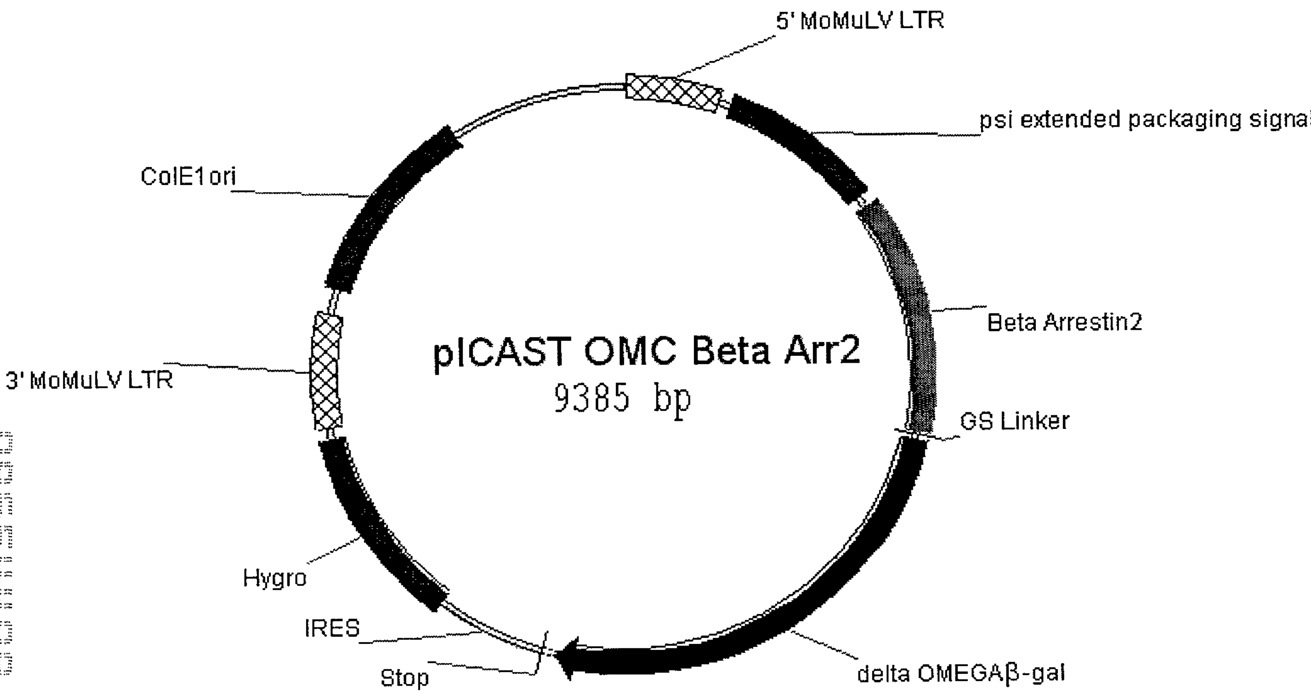


5' MoMuLV LTR
psi extended packaging signal
Beta Arrestin 2
GS Linker
delta ALPHAβ-gal
Stop
IRES
NeoR
3' MoMuLV LTR
ColE1ori
pICAST ALC Beta Arr2
9727 bp

Figure 14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GS Linker
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Hygro
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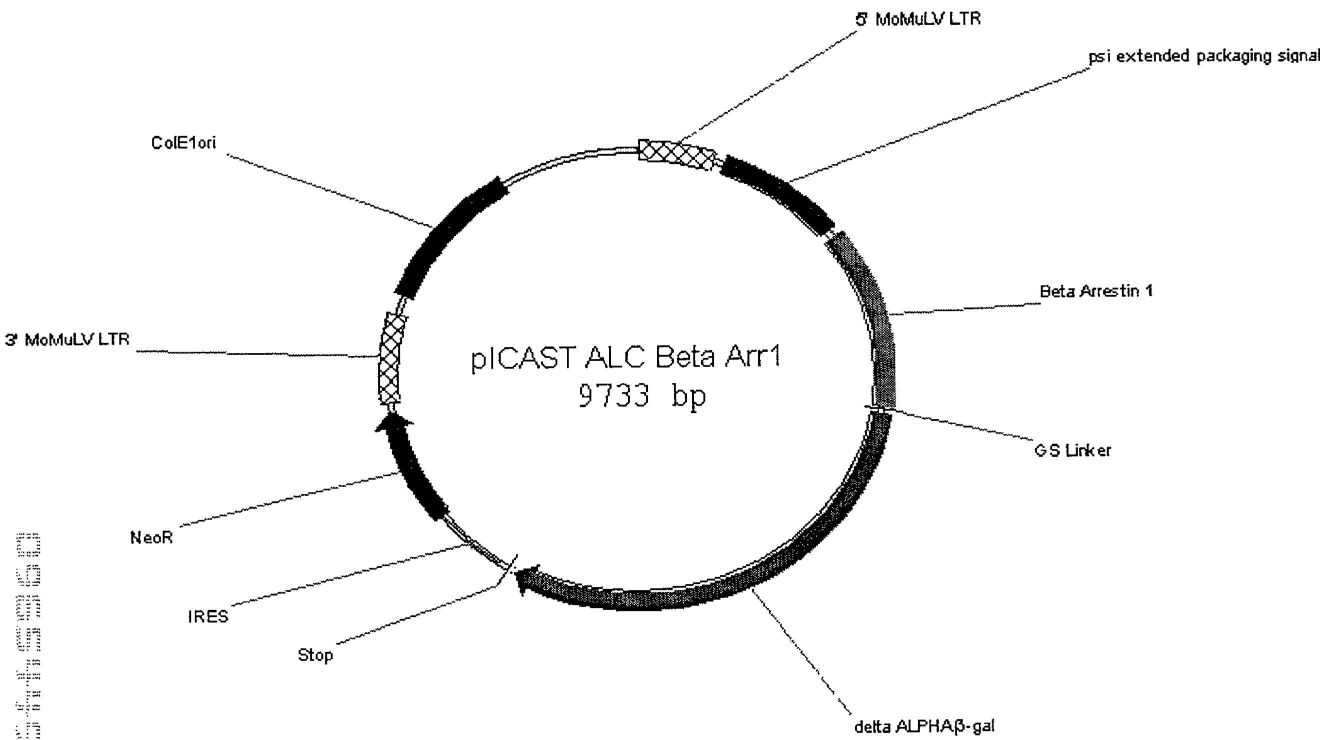
ColE1ori
pICAST OMC Beta Arr2
9385 bp

Figure 15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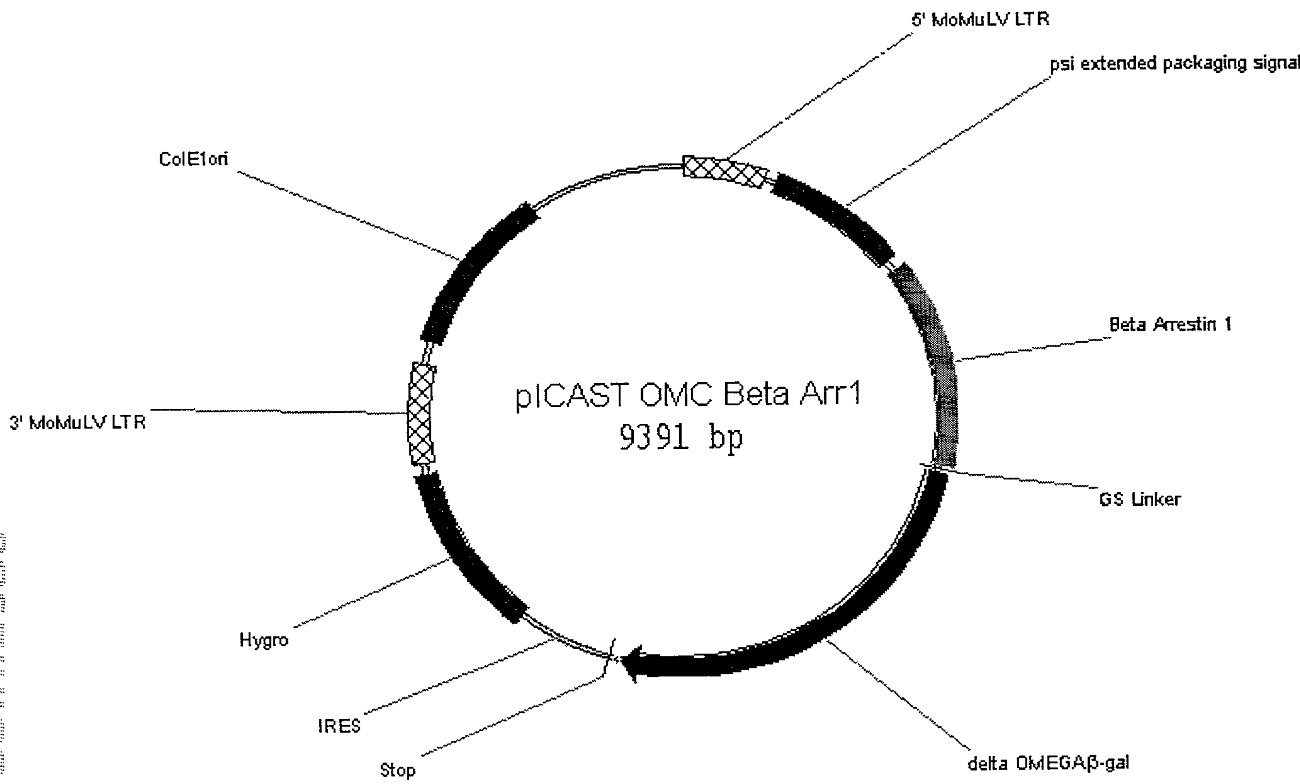
GS Linker
NeoR
IRES
Stop
delta ALPHAβ-gal

Figure 16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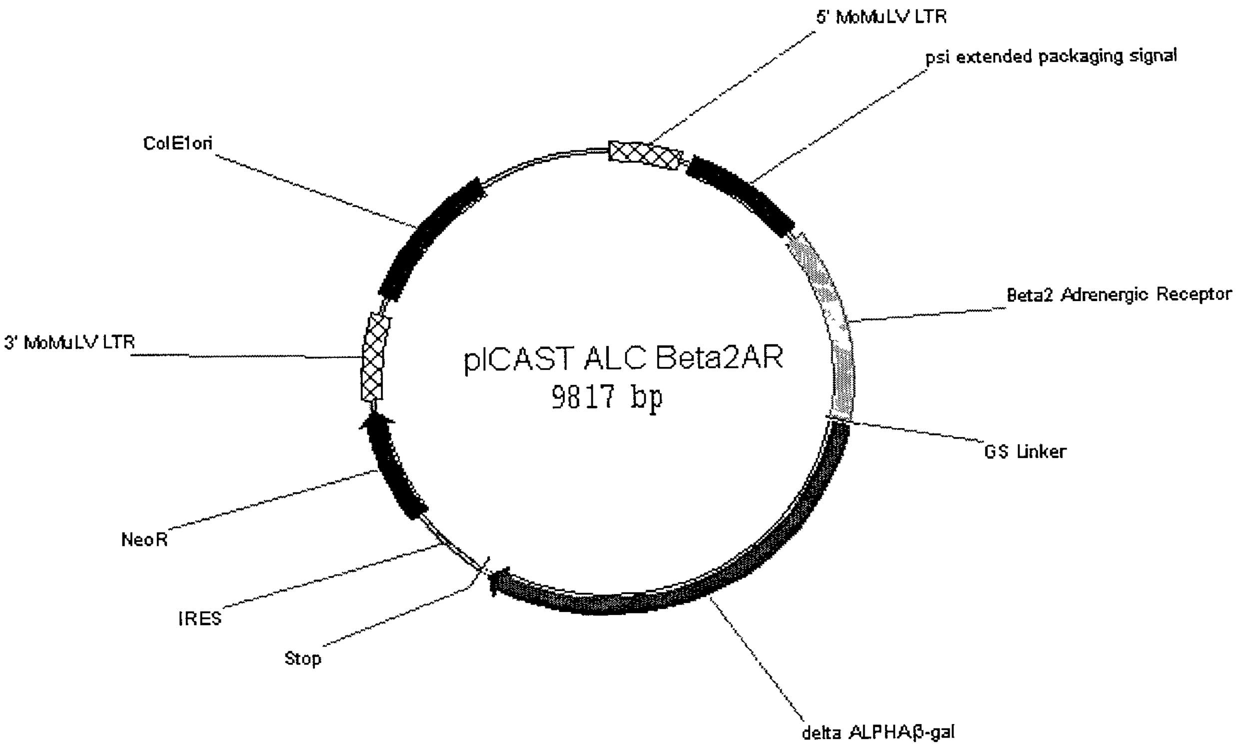
Hygro
IRES
Stop
delta OMEGAβ-gal

Figure 17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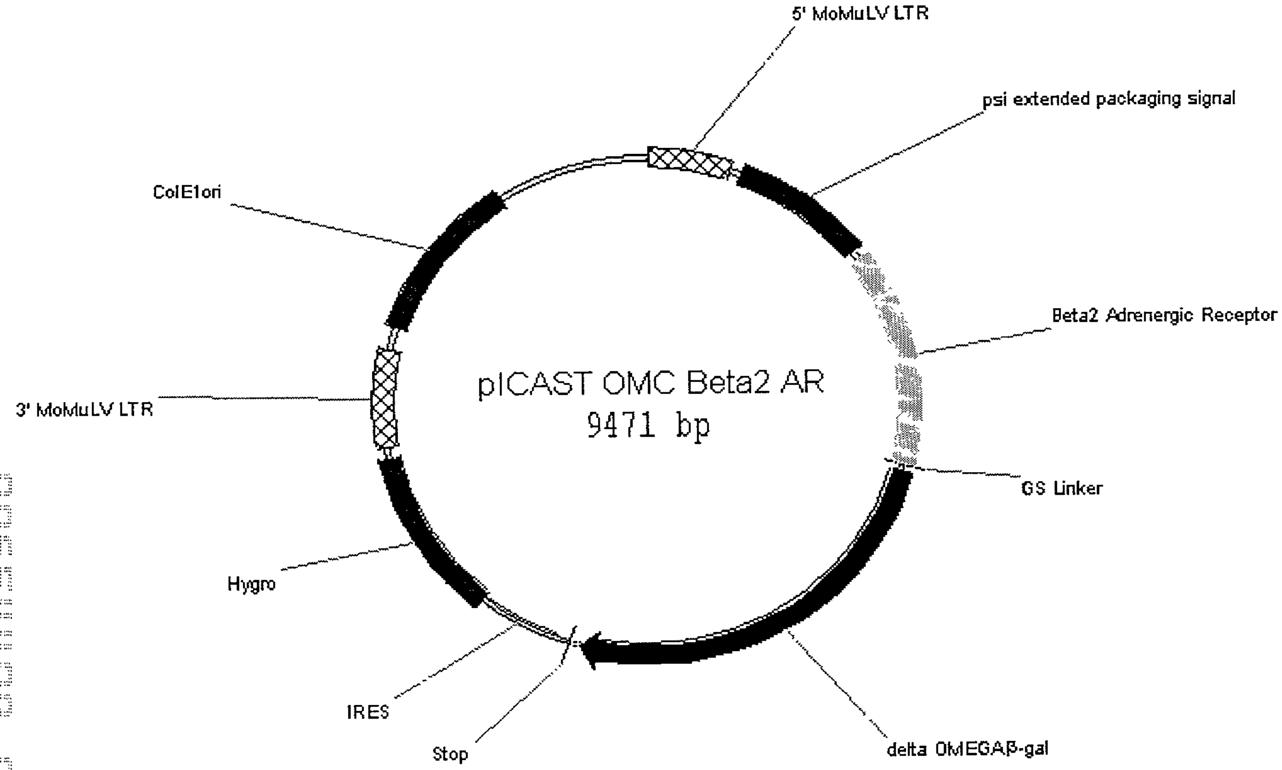
psi extended packaging signal
ColE1ori
Beta2 Adrenergic Receptor
3' MoMuLV LTR
pICAST ALC Beta2AR
9817 bp
GS Linker
NeoR
IRES
Stop
delta ALPHAβ-gal

Figure 18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ColE1ori
Beta2 Adrenergic Receptor
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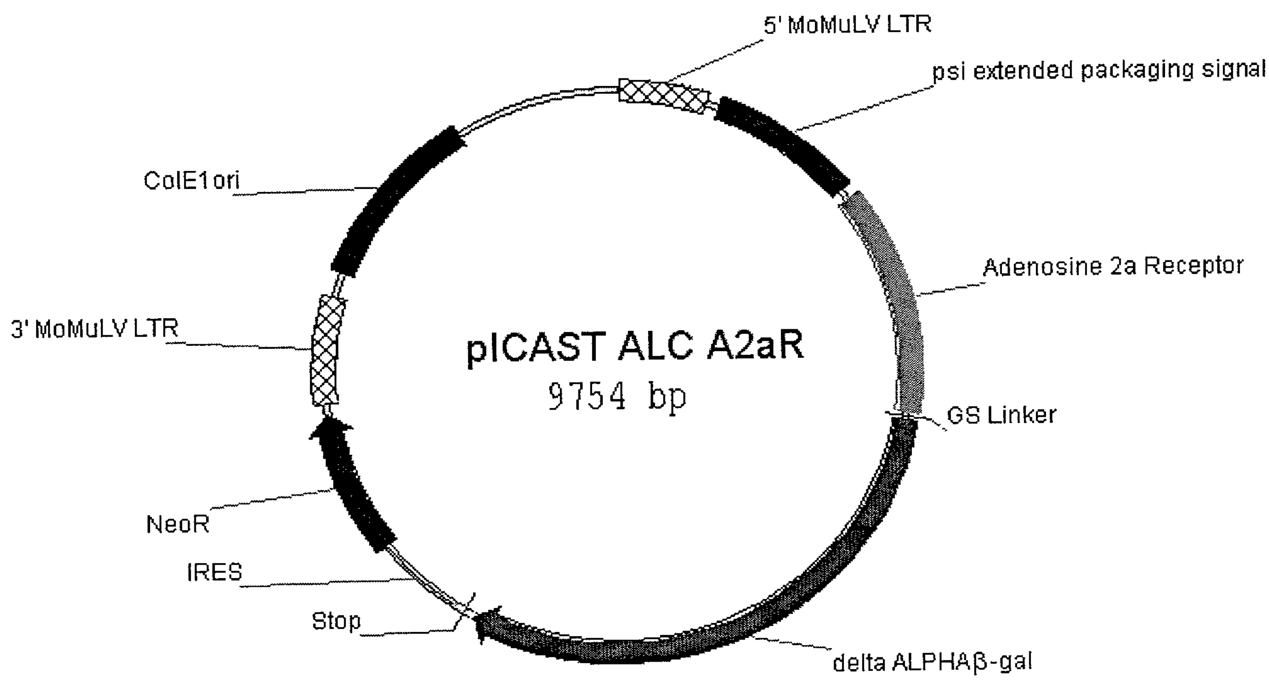
9471 bp
3' MoMuLV LTR
GS Linker
Hygro
IRES
Stop
delta OMEGAβ-gal

Figure 19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psi extended packaging signal
ColE1ori
Adenosine 2a Receptor
3' MoMuLV LTR
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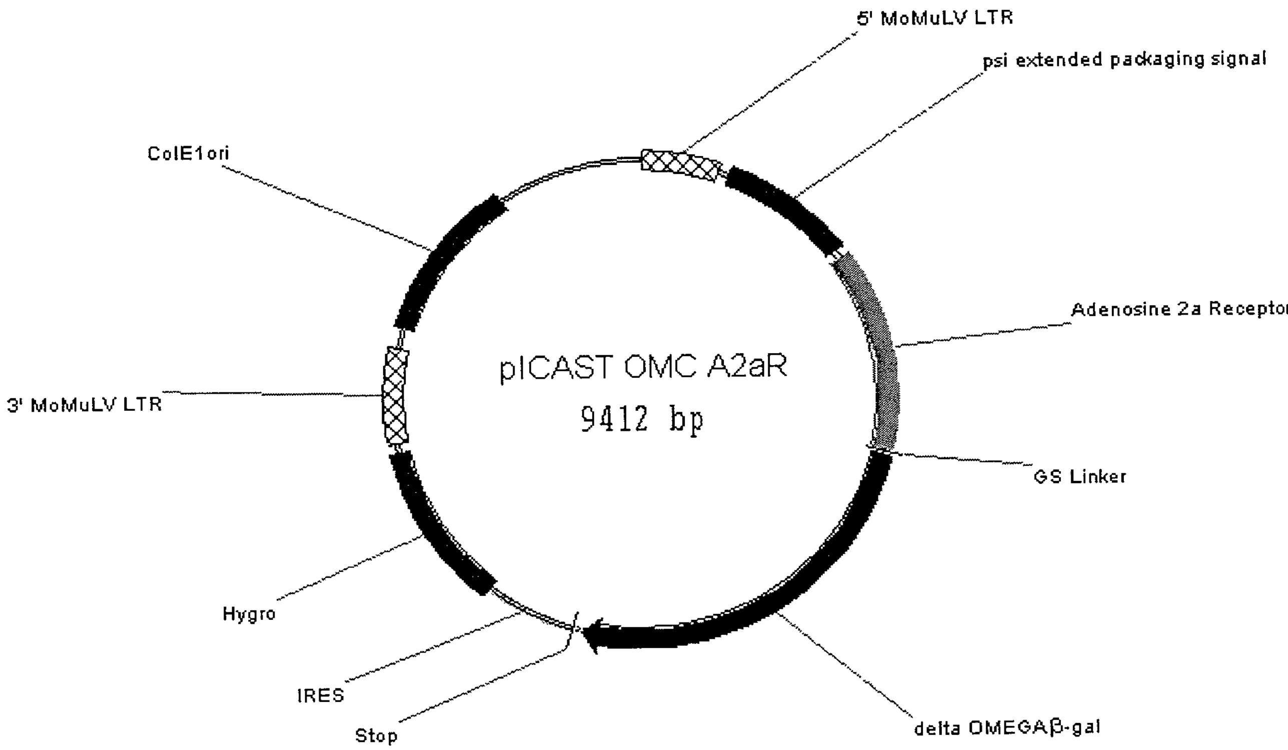
9754 bp
GS Linker
NeoR
IRES
Stop
delta ALPHAβ-gal

Figure 20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ColE1ori
Adenosine 2a Receptor
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9412 bp
3' MoMuLV LTR
GS Linker
Hygro
IRES
Stop
delta OMEGAβ-gal

Figure 21

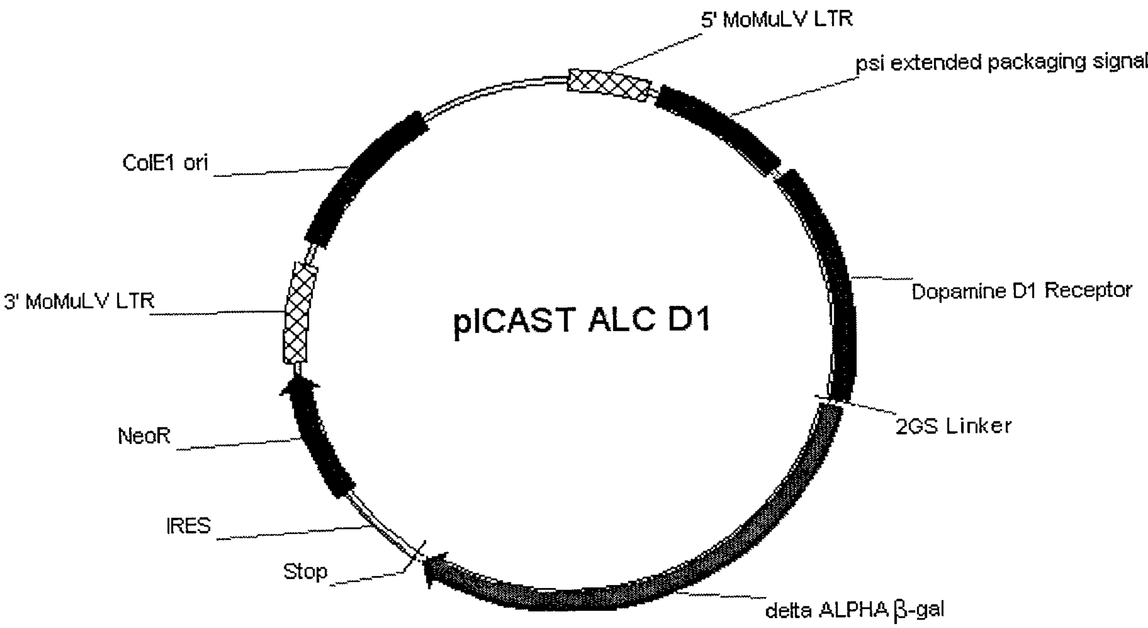
5' MoMuLV LTR
psi extended packaging signal
ColE1 ori
Dopamine D1 Receptor
3' MoMuLV LTR
pICAST ALC D1
2GS Linker
NeoR
IRES
Stop
delta ALPHA β-gal

Figure 22

Functional GPCR Activation Assay and Ligand Fishing for Orphan Receptors by β-galactosidase mutant complementation in ICAST™ System

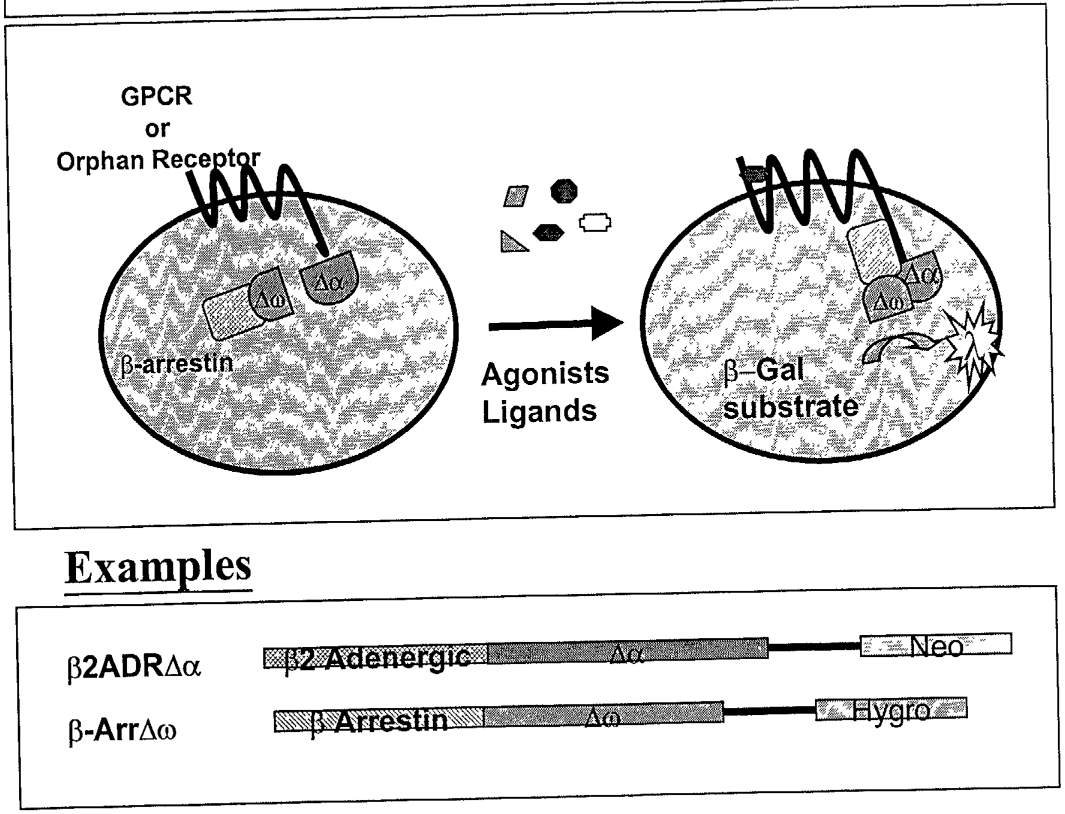

Figure 23

DOCKET NO. 4085-226-27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Michelle A.J. PALMER, et al ART UNIT:
SERIAL NO.: New Application EXAMINER:
FILING DATE: Herewith
FOR: RECEPTOR FUNCTION ASSAY FOR G-PROTEIN COUPLED RECEPTORS AND ORPHAN RECEPTORS BY REPORTER ENZYME MUTANT COMPLEMENTATION

LIST OF INVENTORS' NAMES AND ADDRESSES

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

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A declaration containing all the necessary information will be submitted at a later date.

Respectfully submitted,

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